

Topical Review

Xylitol

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A B S T R A C T

Xylitol is a prevalent sugar substitute found in a wide variety of foods, particularly those labeled as “low carb.” It is found in many medicines and dental products both for its antibacterial activity and to increase palatability. Originally, this toxin was recognized as a problem in dogs following sugarless gum ingestions. Xylitol is generally nontoxic to mammals except for dogs. In the dog, xylitol induces marked increases in insulin production and occasionally hepatopathy. The clinical syndrome is manifested with signs consistent with profound hypoglycemia, hypokalemia, hypophosphatemia, and acute hepatic failure. Treatment relies upon administration of intravenous glucose, hepatic support, and general supportive care.

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Introduction

Xylitol was discovered in the late 19th century; it is also naturally found in low concentrations in a variety of edible plants and mushrooms. Xylitol is a 5-carbon sugar alcohol with many beneficial properties and is primarily used as an artificial sweetener with less than two-thirds the calories of most sugars. Xylitol has many desirable properties for humans including inducing very little insulin release, making it a preferred sugar substitute for individuals intent on consuming low-carbohydrate diets to reduce their glycaemic index. Xylitol does not require insulin to enter cells and is antiketogenic, making it an excellent source of energy for diabetics.¹ Additionally, xylitol inhibits certain bacterial growth.

The 2 major sources of xylitol exposure are food and dental or medical products. Initially, exposures to xylitol in dogs were from “sugar-free” chewing gums. However, with demands from diabetic patients and particularly with the popularity of Atkins-like “low-carb” diets, many foods now contain xylitol. Many foods for “low-carb” diets, including a wide variety of breads, candies, gums, deserts, etc. have xylitol as the sweetener of choice.² It is unfortunate that the Food and Drug Administration no longer requires xylitol be listed as an active ingredient on the label of products in which it is incorporated. The Animal Poison Control Center of the American Society for the prevention of cruelty to animals has reported several cases of xylitol toxicity in dogs with a history of eating sugar-free (“low-carb”) food products, including muffins, cupcakes, gum, and cookies.^{3,4}

Xylitol’s antibacterial activity and palatability has made it popular in a variety of preventive dental products.⁵ It has been added to an expansive list of dental products, particularly high (as much as 35%) in human toothpaste. It has been a problem with dental products where it has been incorporated to increase the palatability of other antimicrobial compounds such as chlorhexidine. Xylitol containing products are safe for cats, and it has been proposed to add it to daily water to prevent feline dental disease; however this would place dogs in the household at risk of a possible life-threatening toxicity.⁶

Xylitol exposures can occur from a variety of therapeutic sources. It has been used as an energy source in parenteral nutrition recipes. The ability to improve palatability has meant that xylitol has been used by both human and veterinary compounding pharmacies. Significantly, xylitol is not required to be listed on the active ingredients list in either veterinary or human medications. Regional poison centers may be able to supply data relative to xylitol concentrations in human medications.

Toxic Dose

Xylitol has a wide margin of safety in mammals with the exception of dogs. The oral lethal dose 50% levels in mice are approximately 20 g/kg. Oral exposures as low as 0.1 mg/kg have induced hypoglycemia in the dog, and levels of 0.5 mg/kg have resulted in hepatotoxicity in some dogs. Oral dose of 4 mg/kg induced clinical signs but did not cause mortality in one study.⁷ Hepatotoxicity may depend more on the individual dog rather than the actual dose received.⁷ The literature reports no cases of xylitol toxicity in cats.

Calculating possible exposure doses is often difficult. The following guidelines with gum exposures have been recommended. When xylitol is the first sugar listed on the label, then the dose should be calculated as the total number of sugar alcohols per piece. If it is not the first sugar alcohol listed on the label then it should be assumed that each piece of gum contains 0.3 g of xylitol. In nongum oral exposures such as baked products or powdered xylitol, then the assumption is that 1 cup xylitol weighs 190 g.³

Toxicokinetics

Rapid absorption occurs in the dog when 1–4 gm/kg of xylitol is orally administered. Insulin levels begin to increase at 20 minutes and are maximized at 40 minutes after ingestion.⁸

Glucose levels began decreasing at 30 minutes and troughed at 60 minutes after ingestion; in this trial, glucose began to rise again at 90 minutes.⁸ In some cases, the onset of clinical signs of hypoglycemia can be delayed up to 24–48 hours postingestion.

Primary metabolism of xylitol occurs in the liver.^{9,10} Xylitol is not renally excreted.

Mechanism of Toxicity

Xylitol toxicity manifests as 2 clinical syndromes, either as hyperinsulinemia or as hepatic necrosis, or a combination of both. It is postulated that hyperinsulinemia is induced by the liver converting xylitol into metabolites that interfere with normal pentose phosphate pathways affecting regulation of insulin synthesis and release.⁸ Xylitol itself may directly stimulate pancreatic β cells to release insulin. Elevated insulin then induces dramatic decreases in blood glucose levels.

Hypokalemia occurs when insulin triggers intracellular transfer of potassium ion into the cells. Hypoglycemia affects red blood cell membranes resulting in rupture and release of bilirubin.

The mechanisms responsible for hepatic injury have not been elucidated. However, it has been postulated that exhaustion of hepatic cellular adenosine triphosphate causes hepatocyte necrosis.¹¹ Coagulation abnormalities can occur secondary to a loss of normal hepatic mass decreasing production of clotting factors or disseminated intravascular coagulation secondary to hepatic necrosis or both.

Clinical Signs

Xylitol can induce 2 possible clinical syndromes which are not mutually exclusive. Most dogs exhibit clinical signs consistent with marked hypoglycemia but some have additional clinical signs relative to an acute hepatopathy. There are some that only develop the hepatopathy.

Clinical signs associated with rapid rises in insulin are hypoglycemia, lethargy, weakness, ataxia, vomiting, hypokalemia and possibly seizures, coma, and death.⁶ Seizures have been seen as early as 30–40 minutes after exposure. The onset of hypoglycemia can be delayed up to 12–48 hours after ingestion.^{7,11,12}

Hepatopathy can develop as early as 1–2 hours postingestion, however, some dogs have delayed onset of 9–72 hours before the clinical signs consistent with acute hepatic failure manifest. In 1 retrospective clinical review, 75% of dogs developing hepatopathy had no clinical signs of hypoglycemia, however, the sample size was small ($n = 8$). These dogs were lethargic and icteric and vomited.

Coagulopathies such as petechia, ecchymosis, and frank hemorrhage (particularly gastrointestinal) may develop secondary to acute hepatic failure.

Minimum Database

As with all possible toxicosis, pretreatment blood samples should be obtained. Recommended laboratory test include a full serum chemistry profile, complete blood count, and electrolytes. An initial blood glucose level should be recorded while awaiting more complete laboratory results.

Serial blood glucose values should be obtained at entry, 30 minutes, 60 minutes, and then hourly for the next 12 hours in suspected xylitol exposures. If clinical evidence of liver dysfunction becomes apparent, serial testing (every 24 hours, for 72 hours) of hepatic enzymes, potassium, phosphorous, and total bilirubin and a close monitoring of coagulation profiles is

required. It is important for coagulation profiles to include platelet counts, partial thromboplastin time, and an activated partial thromboplastin time.

Confirmatory Test

Xylitol is rapidly absorbed and cleared from the body and is not significantly accumulated in tissues making the probability of successful testing unlikely. Laboratory analysis of foods, baits, or stomach ingesta can be done. Recommendations for appropriate samples, handling, preservation techniques, and possibly legal chain of evidence requirements can be supplied by the diagnostic laboratory. This advice should be solicited before sample submission or shipping.

Treatment

Decontamination techniques are generally avoided in xylitol exposures. There is no evidence that activated charcoal binds xylitol efficiently. Emesis induction should be avoided because the toxin is rapidly absorbed, and depression can be an early sign of toxicosis, which increases the risk of aspiration.

In cases suspected to have an exposure of more than 0.1 g/kg, aggressive treatment is recommended. Delayed treatment, even with no clinical signs, increases the risk for catastrophic hepatic necrosis. The victim should be hospitalized, intravenous access established, and dextrose infusion initiated (regardless of initial glucose values).⁷

If the dog is exhibiting hypoglycemia, an initial bolus of 1–2 mL/kg of 25% dextrose followed by 5% dextrose drip should be administered at a rate to maintain normal serum glucose levels. Serum potassium levels less than 2.5 mEq/L may be addressed with the addition of potassium to the intravenous fluids. Serum glucose should be monitored for 24 hours until stabilized without supplementation.^{4,7}

Those dogs with exposures greater than 0.5 g/kg are at higher risk for hepatic involvement regardless of glucose status. Early hepatic support is strongly recommended with antioxidant and protectants including silymarin (20–50 mg/kg/d PO), S-adenosylmethionine (17–20 mg/kg/d PO), or N-acetylcysteine (140–280 mg/kg/initial dose, and subsequent doses of 70 mg/kg QID, either IV or PO).⁷

Coagulopathies are treated with whole blood or plasma transfusions.

Prognosis

Dogs with only hypoglycemia and no clinical evidence of hepatic dysfunction have a good prognosis. Dogs with mild elevations in hepatic enzyme values usually return to normal after several days of supportive care. The presence of significant hepatic involvement, particularly with a rising hyperphosphatemia, has a more guarded prognosis. Evidence of fulminant hepatic failure requires a guarded to poor prognosis.⁴

Differential Diagnosis

Differentials are necessary for both clinical syndromes.

Hypoglycemia

Insulinoma, insulin overdose, hypoadrenocorticism, idiopathic, starvation, overexertion hypoglycemia, juvenile hypoglycemia, and hepatic disease.

Hepatopathy

Infection, *Amanita* mushrooms, blue-green algae, acetaminophen, aflatoxins, and other hepatotoxic compounds.

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