Xylitol Toxicosis in Dogs

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KEYWORDS
• Xylitol • Hypoglycemia • Liver failure • Coagulopathy

The 5-carbon sugar alcohol xylitol is used as a sweetener in many products including gums, candies, and baked goods. In recent years the use of xylitol has increased due to the popularity of low-carbohydrate diets and low–glycemic index foods.[1] Xylitol also prevents oral bacteria from producing acids that damage the surfaces of teeth, leading to its inclusion in toothpaste and other oral care products.[1,2] While xylitol is considered safe in humans, canine ingestions have resulted in severe and life-threatening signs associated with increased insulin secretion leading to hypoglycemia. Acute death due to severe hypoglycemia if untreated is possible, and liver failure may develop 1 to 3 days after xylitol ingestion.

SOURCES

Initially xylitol was used as a sugar substitute during World War II, when sucrose availability was low. During that time, xylitol was derived from birch and other hardwoods.[3] More recently, the sweetener has been used as a sugar substitute for human diabetics. It has a similar sweetness to sucrose and the same number of calories.[4] It has also been eagerly embraced by dental care professionals and the general public due to its anticariogenic properties.[5] Its presence in gum, mints, and candies including gumballs, lollypops, and taffy has been fairly well known for years; however, recently several additional, lesser known products are now also made with xylitol. Veterinarians and pet owners should be aware that this sugar substitute may be found in several common household products, both edible and nonedible, and even in some prescription drugs.

Based on a 2001–2011 search of the ASPCA Animal Poison Control Center's (APCC) product database, xylitol was found to be present in several vitamins (ie, iron, vitamin D, calcium chews, multivitamin tablets, gummy vitamins) and nutritional supplements (coenzyme Q10, 5-hydroxytryptophan, caffeine). Xylitol can also be found in chocolate, baked goods, puddings, syrup, fruit preserves, jellies, nutritional/diet bars, and drink powders. It is also available in its pure form as a sugar substitute

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The authors have nothing to disclose.

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under several different brand names. Xylitol is also used as an ingredient in toothpaste, tooth wipes and towelettes for babies, oral lozenges, moisturizing mouth sprays and gels, and mouthwash because of its ability to prevent cavity formation. It can additionally be found in exfoliating facial wipes, personal lubricants, deodorants, and night creams.

Xylitol is used in medicinal products, most notably both brand-name and generic nicotine gums. It is also found in oral drug suspensions, cold remedies, some sublingual tablets, and nasal sprays.

If an exposure to any of these substances has occurred, the ingestion of xylitol should be considered. It may be listed on product labels using a number of possible synonyms, including Eutrit, Kannit, Klinit, Newtol, xylite, Torch, or Xyliton.[6]

Xylitol is also an ingredient in drinking water additives for dogs and cats. Exposures have been reported to the APCC; however, no evidence of associated xylitol toxicity has been documented to date (ASPCA APCC, unpublished data, 2011). A study involving dogs that received 5 times the recommended xylitol drinking water dose also failed to demonstrate any toxic effects.[7]

TOXICOKINETICS

Xylitol is quickly absorbed from the canine gastrointestinal tract, with peak plasma levels occurring within 30 minutes of ingestion.[8] And 80% of xylitol metabolism occurs in the liver where it is rapidly oxidized to D-xylulose, then metabolized to glucose, glycogen, and lactate via the pentose-phosphate pathway.[9]

Xylitol ingestion in dogs causes a dose-related insulin release that is greater than the response to an equal dose of glucose.[10,11] Peak serum insulin concentrations have been observed to be 6-fold greater following ingestion of xylitol compared to glucose[8] and so may lead to severe hypoglycemia. Xylitol does not cause similar insulin release or blood glucose changes in humans, rats, and horses, although increased insulin releases have been documented in cows, goats, and rabbits.[12] Dogs experimentally dosed with 1 or 4 g of xylitol per kilogram of body weight orally showed sharp increases in plasma insulin concentrations within 20 minutes, peaking at 40 minutes.[13] Another study indicates that xylitol directly stimulates secretion of insulin by pancreatic islet β cells.[8]

The mechanism of action for liver damage in dogs is not fully understood; however, it is thought to be related to either ATP depletion during the metabolism of xylitol leading to hepatic necrosis or the production of hepatocyte-damaging reactive oxygen species.[14] Histopathologic changes observed in 3 dogs with known xylitol toxicosis included severe acute periacinar and midzonal hepatic necrosis with periportal vacuolar degeneration, diffuse hepatic necrosis, and moderate to marked subacute centrilobular hepatocyte loss and atrophy with lobular collapse and disorganization.[14]

TOXICITY

Oral xylitol has a wide margin of safety in most species. The estimated oral LD_{50} of xylitol in rabbits is 4 to 6 g per kilogram of body weight.[15] People consuming more than 130 g of xylitol per day may develop diarrhea but no other abnormalities.[16] Xylitol toxicity has not been reported in cats. Anecdotal reports indicate ferrets have shown evidence of hypoglycemia following ingestion but this has not been confirmed. In fact, the 3 cases of xylitol exposure received by the APCC did not show evidence of hypoglycemia or other adverse effects as reported in dogs.

Based on canine xylitol ingestions reported to the ASPCA APCC, only mild clinical signs of hypoglycemia would be expected with ingestions of less than 100 mg of

xylitol per kilogram of body weight (100 mg/kg), although exposures greater than 50 mg/kg may at least warrant decontamination and blood glucose monitoring. Ingestions involving greater than 500 mg/kg of xylitol in dogs can be associated with hepatic failure.[3]

CLINICAL SIGNS AND LABORATORY CHANGES

A 2001–2011 search of canine xylitol ingestions in the APCC database was performed, limited to cases where the xylitol concentration of the product involved was known and no other potentially toxic exposures were known to have occurred. While ingestions involving mints and 100% xylitol products appear to develop clinical signs quickly (often within 30 minutes potentially due to quick disintegration and release of xylitol from these products), this most recent database search supports previously reported observations that dogs ingesting xylitol-containing gums may not develop clinical signs of hypoglycemia until 12 hours later.[3] These variations in the onset of clinical signs may be related to the formulation-specific product involved and the amount of mastication (chewing) that may have occurred during consumption. When dogs ingest xylitol-containing gums, they usually do not chew/masticate it. This may be the main reason for a delay in onset time of hypoglycemia. Increased mastication of chewing gum would cause an increased likelihood of developing clinical signs relatively more quickly due to an increased release of the product's total available xylitol.[17]

Clinical signs most commonly noted in dogs in the APCC database include vomiting, lethargy, and weakness. Vomiting was most commonly reported with gum ingestions (especially those containing xylitol in the outer coating), mints, and 100% xylitol products, typically within 30 minutes and up to several hours post-exposure. In many of these cases the dogs at least partially self-decontaminated and the xylitol-containing product could be seen in the vomitus.

In cases where lethargy and weakness were reported by the owners, dogs were generally also hypoglycemic on presentation to the veterinary clinic. However, not all animals exhibited hypoglycemia on presentation for veterinary care and sometimes appeared clinically normal on initial examination. Dogs that were presented either nonresponsive or with seizure activity were often hypoglycemic, although in some cases, blood glucose levels performed postictally showed levels within the normal limits. Of the cases reviewed, ingestions involving less than 100 mg of xylitol per kilogram of body weight usually resulted in mild signs. Hyperglycemia has sometimes been reported following xylitol ingestion and may be a result of the Somogyi phenomenon (rebound hyperglycemia) that occurs with insulin overdose.[3]

Some dogs in the APCC database developed mild to moderate hypokalemia or an initial hypophosphatemia, typically within 12 hours of the initial exposure, and appeared to respond well to supplementation. Hyperphosphatemia was instead associated with subsequent hepatic damage and is considered a poor prognostic indicator.

The time at which liver enzyme elevations were first detected generally varied from 4 to 24 hours, but in some cases alanine aminotransferase became elevated in less than 4 hours post-exposure. This early development of mild liver enzyme elevations is consistent with a recent research study performed in China.[13] Dogs in the APCC database that developed hypoglycemia did not always develop evidence of liver damage. Additionally, there were several cases of dogs that developed liver enzyme elevations but not hypoglycemia. Many dogs with elevated liver enzymes did eventually recover, even in some cases where coagulopathies (prolonged

prothrombin and activated partial thromboplastin times) were noted (ASPCA APCC, unpublished data, 2011).

TREATMENT AND MONITORING

On arrival to the veterinary clinic, a baseline blood glucose level should be measured. Emesis should be induced if the dog has not vomited prior to presentation (either by induction or self-decontamination) and no contraindications are indicated by the patient's history or physical examination findings. Apomorphine can be administered either injectably (0.03 mg/kg IV or 0.04 mg/kg IM) or by subconjunctival administration (a crushed ¼ of a 6-mg tablet).[18] If excessive sedation occurs, naloxone can be used as a reversal agent, but the depression associated with apomorphine is generally mild. If the apomorphine is applied to the conjunctiva, a thorough ocular flushing should occur once vomiting has been initiated in order to avoid excessive ocular irritation and retching. As an alternative to apomorphine for the induction of emesis, 3% active hydrogen peroxide can be orally administered at a dosage of 1 to 2.2 mL/kg (generally not exceeding 45 mL as a total dose). If vomiting does not occur after the first dose, it can be repeated once.[19] Additional doses could result in gastric irritation. Vomitus should be thoroughly evaluated for the presence of the ingested xylitol product(s) in order to determine if decontamination was successful.

Emesis is not recommended in patients that have ingested 100% xylitol products more than 30 minutes prior to presentation. Due to the rapid absorption of this form of xylitol, an insulin peak plasma effect can occur within 40 minutes, meaning that clinical signs of hypoglycemia (ataxia, disorientation, and seizures) may develop before or during decontamination.[13] If significant clinical signs and weakness associated with xylitol toxicosis develop during emesis, aspiration may occur.

Activated charcoal is not typically recommended because xylitol is so readily absorbed from the gastrointestinal tract. Also, in vitro studies suggest that activated charcoal binds poorly to xylitol.[20]

Initial blood work should include electrolytes (including potassium), blood glucose, a baseline liver profile, a baseline complete blood count, and a serum phosphorus level. The electrolytes can be repeated in 8 to 12 hours post exposure in several affected animals, and hypokalemia should be corrected as needed. Blood glucose should be evaluated every 2 hours for the first 12 hours and checked more frequently in severely affected patients. Monitoring of blood glucose levels for more than 12 hours may be necessary if hypoglycemia continues to be an issue. Baseline liver enzymes should be reevaluated at 12, 24, and 48 hours later. If liver enzymes become elevated, the patient's coagulation times should be monitored[3] and the complete blood count should be examined for evidence of mild to moderate thrombocytopenia.[14] Serum phosphorus should be evaluated once daily.

An intravenous catheter should be placed in dogs exposed to doses suspected to result in hypoglycemia. If hypoglycemia is identified, an IV dextrose bolus should be administered, followed by parenteral fluids containing 2.5% to 5% dextrose.[3] The dextrose may prevent hypoglycemia in mild intoxications and can be hepatoprotective in patients at risk for hepatic necrosis. *S*-Adenosyl-L-methionine (SAMe) or Denosyl (20 mg/kg per day) and Marin (per label instructions) or milk thistle (50 mg/kg per day) may also be used,[18] although the efficacy of these hepatoprotectants for xylitol toxicosis has not been established. There may also be some benefit for using *N*-acetylcysteine (140 mg/kg PO initially at a 5% concentration, then 70 mg/kg PO at a 5% concentration every 6 to 8 hours for an additional 7 treatments).[18] The efficacy of hepatoprotective effects of *N*-acetylcysteine used in xylitol toxicosis has not been determined. If evidence of hepatic damage develops and the patient's coagulation

profile becomes abnormal, vitamin K_1 therapy should be initiated and plasma transfusions may be considered.

Dogs should be hospitalized for a minimum of 12 to 24 hours post-ingestion because of the risk of delayed-onset hypoglycemia, particularly with chewing gum exposures.[3] If symptoms develop, the patient should receive veterinary care and frequent feedings until the blood glucose level has stabilized. The addition of dietary fiber in the diet may be useful for facilitating the elimination of wrapper materials and packaging that may have been concurrently consumed.

Prognosis is generally good with early decontamination and effective management of hypoglycemia, even in cases where mild liver enzyme elevations have develop. The prognosis becomes more guarded for dogs that develop repeated bouts of profound hypoglycemia (often with central nervous system signs), or significant prolonged liver enzyme elevations, with or without coagulopathy, suggestive of hepatic necrosis. Patients that develop hyperphosphatemia tend to have a poor prognosis for survival; however, even some of these severely affected dogs have successfully recovered.

SUMMARY

Xylitol ingestions in dogs may result in severe hypoglycemia followed by acute hepatic failure and associated coagulopathies. Aggressive treatment may be needed, but the prognosis is generally expected to be good for dogs developing uncomplicated hypoglycemia. Due to increased availability of xylitol-containing products in the market, we will continue to see increased exposures and toxicity in dogs.

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