

New findings on the effects of xylitol ingestion in dogs

Once thought to cause only hypoglycemia in dogs, this sugar substitute has recently been discovered to also produce acute, possibly life-threatening liver disease and coagulopathy. And the number of reported exposures to xylitol has been increasing.

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Xyitol is a sugar alcohol used as a sweetener in many products, including sugar-free gum and mints, nicotine gum, chewable vitamins, oral-care products, and baked goods. It can be purchased in a granulated form for baking and as a sweetener for cereals and beverages. Xylitol is a popular sweetener in Europe (especially Finland, Norway, and Russia) and Japan, and its use as a sweetener in the United States has grown rapidly over the last few years.

While xylitol consumption is considered safe in people, dogs can develop serious, even life-threatening, signs from xylitol ingestion. Xylitol's ability to cause hypoglycemia in dogs has been recognized for almost 40 years, but a recent study has found that xylitol also can cause acute hepatic necrosis.

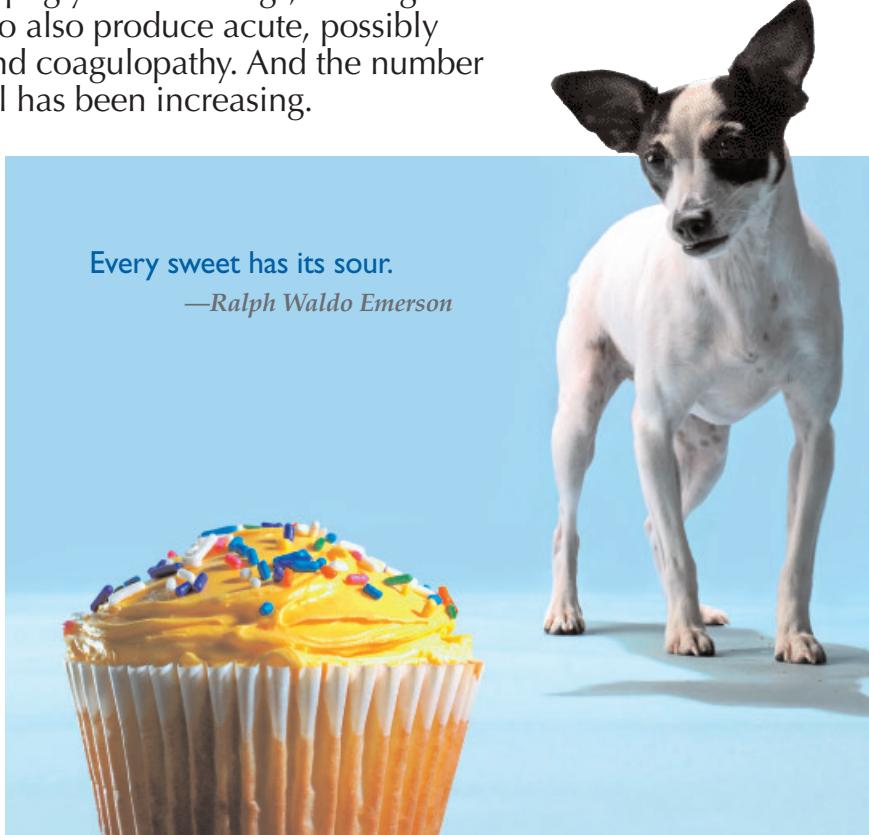
XYLITOL'S HISTORY AND EFFECTS IN PEOPLE

Xylitol was first identified by the German chemist Emil Fisher in 1891; he produced it by hydrogenating D-xylose (wood sugar).¹ It also exists naturally in many edible plants and fungi, such as

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Every sweet has its sour.

—Ralph Waldo Emerson



Photos by Mark McDonald

berries, lettuce, and mushrooms,² and is a metabolite in carbohydrate metabolism as an intermediary during the conversion of L-xylulose to D-xylulose.

Despite being identified in the late 1800s, xylitol was not used commercially until almost half a century later. During World War II, Finland began to produce xylitol because sucrose was unavailable. The process involved extracting xylan (a polysaccharide derived from hardwoods such as birch), hydrolyzing the xylan to its monosaccharide units (D-xylose), and then hydrogenating the D-xylose to produce xylitol. After the war ended and sucrose was again available, xylitol production was curtailed. Commercial in-

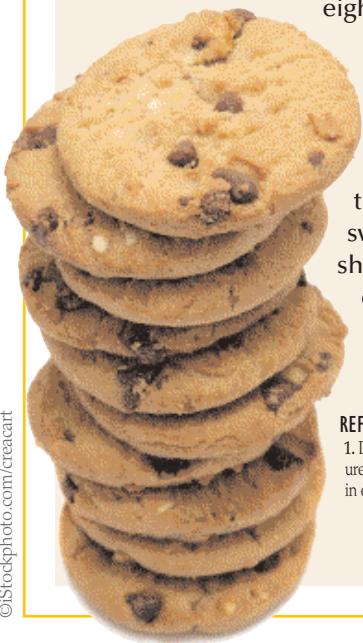
terest in xylitol reawakened in the mid-1970s when large-scale xylitol production became practical. Now more efficient and economical techniques to produce xylitol, such as using corncobs left over from ethanol production, are being developed.²

Xylitol's growing popularity is based on its many beneficial properties. It is as sweet as sucrose on a measure-for-measure basis but has only two-thirds the calories of sugars. Because it causes little insulin release in people, it is considered a good sugar substitute for those on a low-carbohydrate diet and those concerned with the glycemic index of foods.² Since xylitol doesn't re-

Warning to owners: Don't give these sweets to your dogs

The ASPCA APCC study of eight dogs who developed liver failure and coagulopathy because of xylitol ingestion began with one dog—a 4-year-old neutered male Welsh springer spaniel who ate four large chocolate-frosted muffins that contained xylitol.¹ We then reviewed our records from 2003 to 2005 and identified seven more dogs who had eaten xylitol powder or xylitol-sweetened products and developed similar abnormalities. The dogs had eaten a variety of products containing xylitol¹:

- A 3-year-old neutered male standard poodle had eaten five or six cookies
- A 5-year-old spayed female Scottish terrier had eaten 30 pieces of gum
- A 6-year-old spayed female Labrador retriever mix had eaten about 450 g of xylitol powder
- A 7-year-old spayed female miniature dachshund had eaten 100 pieces of gum
- A 4-year-old spayed female Australian shepherd had eaten 12 cupcakes
- An 8-year-old spayed female Labrador retriever had eaten about 140 g of xylitol powder
- A 6-year-old spayed female Dalmatian had eaten eight muffins.



Five of these eight dogs were euthanized or died because of liver failure.

Owners may be watching their diets by using xylitol-sweetened products. But they should also be watching their dogs to ensure that they don't get ahold of products that contain xylitol.

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1. Dunayer EK, Gwaltney-Brant SM. Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. *J Am Vet Med Assoc* 2006;229:1113-1117.

quire insulin to enter cells, it can be used as both an oral and intravenous energy source for diabetics; it is also antiketogenic.³ Experimentally, it increases bone calcification in aged rats; however, the significance of this finding in people has not yet been determined.^{1,2} Finally, xylitol has been shown to inhibit the growth of certain bacteria, which makes it useful in preventing bacterial otitis media in children.^{1,2} It also has anticariogenic properties because it prevents oral bacteria from producing the acids that damage tooth surfaces.^{1,2} For this last reason, it is increasingly being included in sugar-free gum, toothpaste, and other oral-care products.

METABOLISM

Oral absorption of xylitol varies greatly among species. In people and rats, xylitol is absorbed slowly (which increases the risk of osmotic diarrhea associated with excess sugar-alcohol ingestion); between 49% and 95% of oral xylitol is absorbed by people.^{4,5} In dogs, xylitol is rapidly and almost completely absorbed, with peak plasma concentrations occurring at about 30 minutes.⁶

In rats, most xylitol metabolism occurs in the liver. It is rapidly converted to D-xylulose, which is then metabolized via the pentose-phosphate pathway to glucose, glycogen, and, to a lesser extent, lactate.⁷ Virtually no xylitol is excreted in the urine.⁸

TOXICITY AND CLINICAL SIGNS

Oral xylitol has a wide margin of safety in most species. The oral LD₅₀ in mice for xylitol is > 20 g/kg.⁸ In people, consuming > 130 g/day of xylitol will cause diarrhea but no other abnormalities.⁹ But it's a different story in dogs.

The first adverse effect discovered

During the 1960s, researchers trying to determine the feasibility of using xylitol as an energy source in parenteral nutrition made an unexpected discovery. In dogs, intravenous xylitol caused a dose-related release of insulin, greater than the amount released in response to an equal dose of glucose, which could result in a concurrent drop in blood glucose concentrations.^{10,11} Insulin release is also seen with oral dosing of xylitol. In one study in dogs, peak serum insulin concentrations after ingestion of 1 g/kg of xylitol were six times greater than those after ingestion of 1 g/kg of glucose. While serum glucose concentrations rose after ingestion of glucose, the glucose concentrations in the dogs given xylitol orally dropped rapidly and reached a low of about 50 mg/dl one hour after administration.⁶ Cases reported to the ASPCA Animal

Poison Control Center (APCC) indicate that dogs ingesting $> 0.1 \text{ g/kg}$ could develop hypoglycemia.¹²

After xylitol ingestion, vomiting is usually the initial sign. Hypoglycemia may develop within 30 to 60 minutes.¹³ However, in some cases of xylitol gum ingestion, hypoglycemia may be delayed for up to 12 hours (ASPCA APCC Database: Unpublished data, 2003-2006). The clinical signs may progress rapidly from lethargy to ataxia, collapse, and seizure.¹² Initial blood work most often shows profound hypoglycemia¹²; in some cases, though, the dogs have presented with hyperglycemia (ASPCA APCC Database: Unpublished data, 2003-2006). The latter finding may be similar to the Somogyi phenomenon that is seen in cases of iatrogenic insulin overdose.¹⁴ Other common serum chemistry abnormalities include hypokalemia, due to insulin's property of moving potassium into the cell along with glucose,¹⁵ and hypophosphatemia, since insulin can increase cellular permeability to the phosphate ion.¹⁶

Xylitol's effect on blood glucose varies greatly among species. In people, rats, horses, and rhesus monkeys, intravenous xylitol causes little to no increase in insulin release or changes in blood glucose concentrations.¹⁷ On the other hand, intravenous xylitol can cause large insulin release in cows, goats, rabbits, and baboons.^{17,18} Xylitol's effect on insulin release and blood glucose in cats and ferrets is unknown.

A newly discovered danger

Recently, the ASPCA APCC has had reports of some dogs developing elevated liver enzyme activity within 12 to 24 hours after xylitol ingestion.¹² Several of these dogs developed acute liver failure subsequent to xylitol exposure.¹² In a case report on liver failure following xylitol ingestion in eight dogs (see "Warning to owners: Don't give these sweets to your dogs" on page 792), six of the eight dogs did not appear to develop hypoglycemia before the onset of the liver failure.¹² Instead, lethargy and vomiting developed

nine to 72 hours after exposure. Coagulopathy, characterized by prolonged clotting times and petechial, ecchymotic, and gastrointestinal hemorrhages, was also present in the dogs.

Clinicopathologic findings present in all the dogs included elevated alanine transaminase activity (often well beyond the analyzer's range), mild to moderate hyperbilirubinemia, and severely prolonged coagulation times (prothrombin time, activated partial thromboplastin time, or both). Other common findings

the production of reactive oxygen species that can damage cellular components.²¹

ARE OTHER SWEETENERS SAFE IN DOGS?

Other sugar alcohols such as sorbitol and mannitol have little to no effect on blood glucose concentrations or insulin secretion in dogs,⁶ although over-ingestion may result in an osmotic diarrhea. Artificial sweeteners, such as saccharin, aspartame, and sucralose, are generally regarded as safe and



Six of eight dogs did not appear to develop hypoglycemia before the onset of liver failure.

included mild to moderate thrombocytopenia, mild elevation of alkaline phosphatase activity, moderate hypoglycemia (a finding attributed to liver failure rather than xylitol's direct effect on insulin release), and mild to moderate hyperphosphatemia. Hyperphosphatemia was a poor prognostic indicator.

Five of the eight dogs were either euthanized or died. Three dogs were necropsied; two had severe hepatic necrosis, while the third had generalized loss of liver cells with collapse of the liver's architecture.¹² The lowest estimated dose associated with liver failure to date has been 0.5 g/kg (ASPCA APCC Database: Unpublished data, 2003-2006); however, it is not clear at this time whether the effect is dose-related or idiosyncratic.

The cause of the hepatic necrosis is unknown. One possible mechanism is that xylitol and its metabolites deplete adenosine triphosphate in the liver.^{19,20} Without adequate adenosine triphosphate, the liver is unable to maintain normal cellular function, and cellular necrosis results. Another mechanism may involve

should not cause significant illness if large amounts are ingested.²²

DIFFERENTIAL DIAGNOSES

Common causes of hypoglycemia in dogs include parenteral insulin overdose, oral hypoglycemic drugs such as glipizide or glyburide, juvenile hypoglycemia, hunting dog hypoglycemia, pancreatic beta-cell tumor (insulinoma), and idiopathic causes.²³ Acute hepatic necrosis in dogs can be caused by ingestion of acetaminophen, aflatoxins, *Amanita phalloides* and similar hepatotoxic mushrooms, blue-green algae, iron, and sago palms (*Cycas* species).^{24,25} In addition, acute hepatic necrosis can be caused by infectious diseases (e.g. infectious canine hepatitis, leptospirosis, mycoses, toxoplasmosis), trauma, and heatstroke.²⁵

TREATMENT

Based on experience at the ASPCA APCC, dogs ingesting $> 0.1 \text{ g/kg}$ of xylitol should be considered at risk for developing hypoglycemia, while doses of $> 0.5 \text{ g/kg}$ may be hepatotoxic. Calculating the xylitol dose for gum products

can be difficult. While some gum products specify their xylitol content, it is more likely that only the total sugar alcohol content will be listed on the label. In most gum products, several different sugar alcohols (including sorbitol, isomalt, maltitol, and mannitol) may be present, making it difficult to determine xylitol content. If xylitol is the first sugar alcohol in the ingredient list, then the dose should be based on the total amount of sugar alcohols per piece even though this will result in an overestimation of the xylitol dose. If xylitol is not the first listed sugar alcohol, I recommend that 0.3 g of xylitol per piece of gum be used to estimate the xylitol dose. For powdered xylitol and home-baked goods, 1 cup of xylitol weighs about 190 g.

Since the onset of signs can be rapid, emesis should be attempted only if the animal is asymptomatic. Activated charcoal is not likely to be beneficial. In one *in vitro* experiment, activated charcoal was found to bind a low percentage of xylitol, and the binding was pH-dependent.²⁶ If a dog ingests between 0.1 and 0.5 g/kg of xylitol, hospitalize the dog and obtain baseline glucose, potassium, phosphorus, and total bilirubin concentrations; liver enzyme activities; and coagulation measurements. Monitor blood glucose concentrations every one to two hours for at least 12 hours, and recheck the other tests every 24 hours for at least 72 hours.

If hypoglycemia develops, administer a 1- to 2-ml/kg bolus of 25% dextrose intravenously followed by intravenous fluids containing 2.5% to 5% dextrose in order to maintain normal glucose concentrations. Correct severe hypokalemia (< 2.5 mEq/L) by adding potassium to the fluids. Treatment may be needed for 12 to 24 hours or until glucose concentrations can be maintained without supplemental dextrose.

For exposures of > 0.5 g/kg, the treatment is the same as outlined above except I recommend that dextrose treatment be started immediately, whether or not hypoglycemia has occurred. Liver protectants and antioxi-

dants such as N-acetylcysteine (140 to 280 mg/kg loading dose followed by 70 mg/kg intravenously or orally q.i.d.), S-adenosylmethionine (Denosyl—Nutramax; 17 to 20 mg/kg/day orally), silymarin (Marin [Silybin]—Nutramax; 20 to 50 mg/kg/day orally), or vitamin E (100 to 400 IU orally b.i.d.) may be useful, although their efficacy in this tox-

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Doses of > 0.5 g/kg of xylitol may be hepatotoxic.

cosis has not been established. Plasma transfusions, blood transfusions, or both may be needed if a coagulopathy develops.

PROGNOSIS

The prognosis for uncomplicated hypoglycemia is good with prompt treatment. Mild increases in liver enzyme activities usually resolve within a few days with supportive care. On the other hand, if severe elevation of liver enzyme activities, hyperbilirubinemia, and coagulopathy develop, the prognosis is guarded to poor. In addition, hyperphosphatemia appears to be a poor prognostic indicator.

CONCLUSION

Xylitol is an emerging toxicosis in the United States. The number of products that contain xylitol have been growing steadily over the past few years, as have the exposures to xylitol reported to the ASPCA APCC. Because of the potential for rapid onset of signs, treatment should be instituted in all cases in which a dog may have ingested > 0.1 g/kg of xylitol. ♦

You might laugh.
You might cry.
You might even
learn something.

CE

You can earn two hours of Continuing Education credit from Kansas State University by answering the following questions on xylitol toxicosis in dogs. Circle only the best answer for each question, and transfer your answers to the form on page 798.

Article #1

- 1.** Which is true of xylitol?
 - a. It can prevent cavities in teeth.
 - b. It can prevent bacterial otitis media in children.
 - c. It can increase bone calcification in rats.
 - d. It is antiketogenic.
 - e. All of the above

- 2.** What is the threshold dose of xylitol that can cause hypoglycemia in dogs?
 - a. 0.05 g/kg
 - b. 0.1 g/kg
 - c. 0.5 g/kg
 - d. 1 g/kg
 - e. 5 g/kg

- 3.** What is the threshold dose of xylitol that can be hepatotoxic in dogs?
 - a. 0.05 g/kg
 - b. 0.1 g/kg
 - c. 0.5 g/kg
 - d. 1 g/kg
 - e. 5 g/kg

- 4.** Which is not a common product that contains xylitol?
 - a. Baked goods
 - b. Chewable vitamins
 - c. Sugar-free gum
 - d. Sugar-free ice cream
 - e. Toothpaste

- 5.** Which is not a clinicopathologic abnormality seen in dogs ingesting xylitol and experiencing liver failure?
 - a. Hypercalcemia
 - b. Elevated alanine transaminase
 - c. Severely prolonged coagulation times
 - d. Hyperbilirubinemia
 - e. Hyperphosphatemia

- 6.** In a study in dogs, how much higher were the dogs' serum insulin concentra-

tions after ingesting 1 g/kg of xylitol compared with their insulin concentrations after ingesting 1 g/kg of glucose?

- a. Two times higher
- b. Three times higher
- c. Five times higher
- d. Six times higher
- e. Eight times higher

- 7.** How many grams does one cup of powdered xylitol equal?
 - a. 100 g
 - b. 130 g
 - c. 170 g
 - d. 190 g
 - e. 210 g

- 8.** Which statement regarding therapy for xylitol toxicosis in dogs is false?
 - a. Emesis should be attempted in every animal.
 - b. Blood glucose concentrations should be measured every one to two hours for at least 12 hours.
 - c. Antioxidants may be beneficial.
 - d. Intravenous dextrose therapy should be initiated immediately in all cases.
 - e. Both A and D

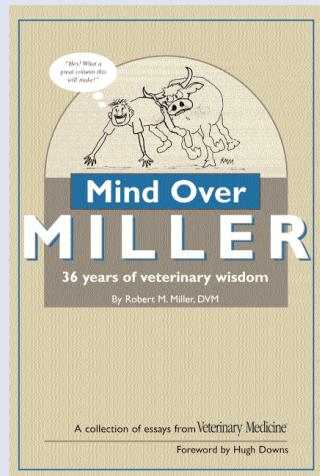
- 9.** Which is not a differential diagnosis for hepatic necrosis in dogs?
 - a. Xylitol ingestion
 - b. Sorbitol ingestion
 - c. Iron ingestion
 - d. Acetaminophen ingestion
 - e. Both B and D

- 10.** How quickly can hypoglycemia develop in dogs after xylitol ingestion?
 - a. Five to 10 minutes
 - b. 15 to 20 minutes
 - c. 30 to 60 minutes
 - d. One to two hours
 - e. Two to three hours

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