Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs

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Case Description—8 adult dogs were evaluated for treatment of lethargy and vomiting after ingestion of xylitol, a sugar alcohol used as a sweetener in various products.

Clinical Findings—In addition to vomiting and lethargy, 5 of the dogs had widespread petechial, ecchymotic, or gastrointestinal tract hemorrhages. Common clinicopathologic findings included moderately to severely high serum activities of liver enzymes, hyperbilirubinemia, hypoglycemia, hyperphosphatemia, prolonged clotting times, and thrombocytopenia. Necropsies were performed on 3 dogs and severe hepatic necrosis was found in 2. In the third dog, histologic examination revealed severe hepatocyte loss or atrophy with lobular collapse.

Treatment and Outcome—Treatments varied among dogs and included IV administration of fluids; plasma transfusions; and, if indicated, administration of dextrose. Three dogs were euthanatized, 2 dogs died, 2 dogs made a complete recovery, and 1 dog was recovering but was lost to follow-up.

Clinical Relevance—Although xylitol causes hypoglycemia in dogs, hepatic failure after ingestion has not previously been reported. Because an increasing number of consumer products contain xylitol, clinicians should be aware that ingestion of xylitol can have serious, life-threatening effects. (*J Am Vet Med Assoc* 2006;229:1113–1117)

ABBREVIATIONS

ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
PT	Prothrombin time
PTT	Partial thromboplastin time
APCC	Animal Poison Control Center
AST	Aspartate aminotransferase
LDH	Lactate dehydrogenase

A 4-year-old 28.5-kg (62.7-lb) neutered male Welsh Springer Spaniel was evaluated at a veterinary emergency clinic for sudden onset of lethargy. Approximately 1 to 2 hours prior, the dog had ingested 4 large chocolate-frosted muffins sweetened with xylitol. The muffins contained approximately 454 g (1 lb) of xylitol, so the xylitol dose was approximately 15.9 g/kg (7.23 g/lb) of body weight. The dog was extremely lethargic. Rectal temperature was 38.5°C (101.3°F), heart rate was 134 beats/min, and respiratory rate was 22 breaths/min. The mucous membranes were pink and tacky with capillary refill time within reference range. The abdomen was flaccid, and signs of abdominal pain were not elicited. The dog was severely hypoglycemic (blood glucose concentration [measured by use of a glucose meter], 18 mg/dL). An IV bolus of dextrose (dose not specified) was administered, and lactated Ringer's solution and 5% dextrose solution with 20 mEq of KCl/L was administered IV. Amoxicillin (23 mg/kg [10.5 mg/lb], SC, q 12 h) was also administered.

Blood was drawn at the time of admission. Hematologic abnormalities included mildly high Hct (49%; reference range, 24% to 45%), high hemoglobin concentration (15.7 g/dL; reference range, 8 to 15 g/dL), and mild thrombocytopenia (159×10^9 platelets/L; reference range, 175 to 500×10^9 platelets/L). Serum biochemical analyses revealed severe hypoglycemia (44.7 mg/dL; reference range, 77 to 125 mg/dL), moderate hypophosphatemia (1.8 mg/dL; reference range, 2.5 to 6.8 mg/dL), mild hypokalemia (3.4 mEq/L; reference range, 3.6 to 5.5 mEq/L), slightly high activity of ALT (144 U/L; reference range, 10 to 100 U/L), slightly high creatinine concentration (3.0 mg/dL; reference range, 0.5 to 1.8 U/L), and low BUN (6.4 mg/dL; reference range, 7 to 27 mg/dL).

Two hours after admission, blood glucose concentration (measured by use of a glucose meter) was 37 mg/dL; another bolus of dextrose was administered. Three hours later, blood glucose concentration was 84 mg/dL, and at discharge, 5 hours later, it was 60 mg/dL.

The dog was transferred to another veterinarian. At that time, the dog was vomiting. On the second day after ingestion of the xylitol, the dog was again hypoglycemic (blood glucose concentration, 48 mg/dL), so additional dextrose was administered. Serum was icteric. Serum activity of ALP was slightly high (284 U/L; reference range, 23 to 212 U/L), activity of ALT was greater than the upper analytic limit of the analyzer, BUN was within reference range (24 mg/dL; reference range, 7 to 27 mg/dL), creatinine concentration was slightly high (2.9 mg/dL; reference range, 0.5 to 1.8 mg/dL), hyperglycemia was mild (145 mg/dL; reference range, 77 to 125 mg/dL), hyperphosphatemia was marked (13.5 mg/dL; reference range, 2.5 to 6.8 mg/dL), and hyperbilirubinemia was moderate (3.0 mg/dL; reference range, 0.0 to 0.9 mg/dL).

Later in the day, the dog was transferred to a specialty clinic, at which time the dog was mildly hypothermic (rectal temperature, 37.7°C [100.0°F]). Epistaxis, oral hemorrhage, and bloody feces were seen. At this time, hematologic abnormalities included low absolute lymphocyte count (333 cells/µL; reference range, 1,000 to 4,800 cells/µL) and moderate thrombocytopenia (98.7×10^3 platelets/L; reference range, 164 to 510×10^3 platelets/L). Thrombocytopenia was con-

firmed by use of a manual count (140×10^3 platelets/L). Also detected were severe hypoglycemia (26 mg/dL; reference range, 60 to 125 mg/dL), moderate hyperphosphatemia (12.1 mg/dL; reference range, 2.1 to 6.3 mg/dL), mild hypokalemia (3.4 mEq/L; reference range, 4.0 to 5.6 mEq/L), mild hypochloremia (92 mEq/L; reference range, 105 to 115 mEq/L), slightly high creatinine concentration (2.3 mg/dL; reference range, 0.4 to 1.8 mg/dL), high total bilirubin concentration (4.2 mg/dL; reference range, 0.0 to 0.4 mg/dL), moderately high ALP activity (405 U/L; reference range, 10 to 150 U/L), high creatine kinase (1,408 U/L; reference range, 10 to 200 U/L), moderately high γ-glutamyltransferase activity (35 U/L; reference range, 0 to 14 U/L), and high anion gap (40.4 mEq/L; reference range, 10 to 25 mEq/L). Activity of ALT was not abnormal (19 U/L; reference range, 5 to 60 U/L). Coagulopathy with high PT (> 60 seconds; reference range, 5.8 to 12.8 seconds), high PTT (> 60 seconds; reference range, 10.9 to 23.9 seconds), and low fibrinogen concentration (< 50 mg/dL; reference range, 55 to 360 mg/dL) were evident.

Several fresh-frozen plasma transfusions were administered (total volume, 250 mL); nevertheless, the dog's PT and PTT remained longer than the analyzer's range. Administration of vitamin K1 (2.5 mg/kg [1.14 mg/lb], SC, q 12 h) was initiated. Fluids were administered (0.9% NaCl with 2.5% dextrose, 50 mEq of KCl/250 mL, and 5.8 mg of metoclopromide/250 mL) at 100 mL/h. The dog's CNS status worsened; signs such as inappropriate mentation and an isolated seizure were seen. Enemas with lactulose were performed every 12 hours, and metronidazole (8.8 mg/kg [4.0 mg/lb], IV, q 12 h) was administered to treat possible hepatoencephalopathy.

On the third day after ingestion of the xylitol, the dog became progressively worse. An additional 300 mL of fresh-frozen plasma was administered. The dog developed severe tachycardia (heart rate, 200 beats/min). Arterial oxygen saturation decreased to 85% but improved to 90% by use of an oxygen mask. The dog's rectal temperature increased to 41.1°C (106.0°F). The veterinarian suspected possible aspiration pneumonia, a reaction to plasma transfusion, or both. Diphenhydramine (0.9 mg/kg [0.41 mg/lb], SC), ampicillin (22.8 mg/kg [10.4 mg/lb], IV), and enrofloxacin (5.3 mg/kg [2.41 mg/lb], IV) were administered. The dog became hypotensive (systolic pressure, 92 mm Hg; diastolic pressure, 40 mm Hg; mean arterial pressure, 70 mm Hg). A bolus of fluids was administered; shortly afterward, the dog vomited a large amount of blood. Because of the dog's rapidly deteriorating condition, the owner permitted euthanasia.

Necropsy revealed severe subcutaneous and visceral ecchymotic hemorrhages, moderate hemomediastinum, mild hemoperitoneum, marked pulmonary congestion and edema, and moderate icterus. Histologic examination revealed severe acute periacinar and midzonal hepatic necrosis with periportal vacuolar degeneration. The pathologist considered the lesions to be consistent with exposure to a hepatotoxic agent. In addition, there was mild subacute neutrophilic and lymphoplasmacytic cholangiohepatitis

with mild biliary hyperplasia. Widespread hemorrhage was seen in the kidneys, stomach, small intestine, pancreas, myocardium, and lymph nodes.

A review of the American Society for the Prevention of Cruelty to Animals APCC's computerized database for records from 2003 to 2005 revealed 7 additional cases of xylitol ingestion in which dogs developed clinical signs similar to those of the previously described dog of this report. A 3-year-old 31.8-kg (70.0-lb) neutered male Standard Poodle ingested 5 or 6 cookies[a] (estimated xylitol dose, 1.4 to 2.0 g/kg [0.6 to 0.9 g/lb] of body weight); the dog developed clinical signs after approximately 24 hours and died approximately 2 days after the ingestion. A 5-year-old 7.4-kg (16.3-lb) spayed female Scottish Terrier ingested 30 pieces of gum[b] (estimated xylitol dose, 7.0 g/kg [3.2 g/lb] of body weight); the dog developed clinical signs after approximately 24 hours and was euthanatized 5 days after the ingestion because of poor response to treatment. A 6-year-old 32.6-kg (71.7-lb) spayed female Labrador Retriever–mixed-breed dog ingested 454 g of xylitol powder (xylitol dose, 13.9 g/kg [6.3 g/lb] of body weight); the dog developed clinical signs after approximately 24 hours and died approximately 36 hours after the ingestion. A 7-year-old 5.0-kg (11.0-lb) spayed female Miniature Dachshund ingested 100 pieces of gum[c] (estimated xylitol dose, 16.0 g/kg [7.3 g/lb] of body weight); the dog developed clinical signs 72 hours after the ingestion and completely recovered. A 4-year-old 17.3-kg (38.1-lb) spayed female Australian Shepherd ingested 12 xylitol-sweetened cupcakes (xylitol dose unknown); the dog developed clinical signs after approximately 8 hours and was euthanatized 4 days after the ingestion because of poor response to treatment. An 8-year-old 34.1-kg (75.2-lb) spayed female Labrador Retriever ingested 143 g (5.0 oz) of xylitol powder (xylitol dose, 4.1 g/kg [1.9 g/lb] of body weight); the dog developed clinical signs 2 hours after ingestion and was recovering when lost to follow-up. A 6-year-old 23.6-kg (51.9-lb) spayed female Dalmatian ingested 8 muffins sweetened with a total of 117 g of xylitol (xylitol dose, 5.0 g/kg [2.3 g/lb] of body weight); the dog developed clinical signs 9 hours after the ingestion and completely recovered.

Primary clinical signs at evaluation were lethargy and vomiting. One dog was recumbent, nonresponsive, and profoundly hypoglycemic approximately 2 hours after ingesting the xylitol. Four dogs developed signs of coagulopathy, including petechial and ecchymotic hemorrhages of the mucous membranes and skin, bloody feces, and continued hemorrhage from venipuncture sites. One dog had a seizure late in the course of the toxicosis.

Clinicopathologic changes in the 7 additional dogs were similar to those seen in the first dog in this report. Values for all analyses were not reported to the APCC for all 7 additional dogs. All 7 dogs had marked increase in serum activity of ALT (1,000 U/L to > 10,000 U/L), mild to moderate hyperbilirubinemia (1.0 to 5.0 mg/dL; mean, 4.1 mg/dL), and moderate to marked prolonged PT (36 to > 100 seconds). Mild to moderate thrombocytopenia was detected in 6 of 6 dogs in which this variable was reported (75 to 169×10^3 platelets/L; mean,

137×10^3 platelets/L), marked prolongation of the PTT in 4 of 4 dogs (> 100 seconds), mild to moderately high serum activity of ALP in 5 of 6 dogs (78 to 716 U/L; mean, 334 U/L), moderate to severe hypoglycemia in 4 of 5 dogs (30 to 94 mg/dL; mean, 54.6 mg/dL), mild to moderate hyperphosphatemia in 3 of 4 dogs (3.6 to 10.1 mg/dL; mean, 6.9 mg/dL), markedly high serum activity of AST in 1 dog (> 25,000 U/L), both decreased fibrinogen (< 50 mg/dL; reference range, 150 to 400 mg/dL) and high concentration of D-dimers (500 to 1,000 ng/mL; reference range, < 250 ng/mL) in 1 dog, and high concentration of fibrin degradation products (2,000 ng/dL; reference range, < 250 ng/dL) in 1 dog.

Treatments used for these 7 dogs were similar to those used for the first dog in this report. These treatments included IV administration of fluids, plasma transfusion, and antimicrobials, and dextrose in dogs that developed hypoglycemia. Despite aggressive treatment, 4 of the 7 dogs died or were euthanatized.

Necropsy was performed in 2 of the 7 dogs and revealed widespread hemorrhage including hemoabdomen, petechial and ecchymotic serosal hemorrhages of the abdominal organs, and hemorrhage into the lumen of the stomach and intestines. One dog had hemomediastinum, and icterus was evident in both dogs. One dog had severe diffuse hepatic necrosis, mild diffuse lymphoplasmacytic enteritis, and focal pulmonary atelectasis and congestion; the pathologist considered the hepatic changes consistent with acute hepatotoxicosis. The other dog had moderate to marked subacute centrolobular hepatocyte loss and atrophy, lobular collapse and disorganization, bile stasis, bile duct hyperplasia, severe subacute ulcerative gastritis with vasculitis and fungal organisms, lymphoid depletion in the spleen and mesenteric lymph nodes, pulmonary edema and hemorrhage, and mild acute renal tubular necrosis; the pathologist considered the liver findings consistent with exposure to a hepatotoxin. Diagnostic evaluation for viral and bacterial infection was not performed in any of the cases.

Discussion

Xylitol is a 5-carbon sugar alcohol (a pentitol). It occurs in small amounts as a natural intermediary during the conversion of L-xylulose to D-xylulose.[1] It also occurs in low concentrations in fruits and vegetables.[2] Xylitol first came into widespread use in Finland during World War II as a substitute for sucrose.[3] In commercial xylitol production, D-xylulose is extracted from wood chips, corn cobs, or other plant material and is chemically processed to produce xylitol. Microbial production methods are presently being developed that may make the process less expensive.[3]

Recently introduced into the United States, xylitol has been advocated for use by diabetics and low-carbohydrate dieters[3] and is anticariogenic.[3] Xylitol is most commonly found in baked goods, desserts, toothpaste, other oral care products, and sugar-free gums and candies. It can be purchased as granulated powder for cooking and baking.[3]

In 2002, the APCC began receiving calls concerning ingestion by dogs of products containing xylitol. In 2004, one of the authors reported on the effects of xylitol ingestion in a dog.[4] Whereas humans who ingest xylitol have little or no increase in insulin secretion or change in blood glucose concentrations, dogs that ingest xylitol have a rapid, severe increase in blood insulin concentration. After ingestion, dogs can develop vomiting, weakness, ataxia, hypoglycemia, hypokalemia, and seizures within 30 to 60 minutes.[4]

More recently the APCC has received reports of dogs with high serum activities of liver enzymes after ingestion of xylitol. Some of these dogs also have developed hyperbilirubinemia and coagulopathies suggestive of severe acute hepatic necrosis, which has not previously been associated with ingestion of xylitol in dogs or any other animals.

In most species, overconsumption of sugar alcohols such as xylitol can lead to diarrhea and increased intestinal gas.[5] In mice, the oral LD_{50} for xylitol is > 20 g/kg. Mice administered a fatal dose of xylitol develop ataxia and prostration; the major lesions are confined to the gastrointestinal tract.[6] Rabbits administered 10 g of xylitol/kg orally have high serum activity of AST, but there has been no mention of hepatic injury.[7] Various studies of acute and chronic xylitol ingestion by humans do not reveal any effect on serum liver enzyme values; diarrhea has been the major effect at high doses.[5] Studies of both short-term and long-term xylitol administration to rats do not consistently reveal substantial increases in liver enzyme activities or hepatic histologic changes.[6] One study[8] in rats revealed high bilirubin concentration and serum activity of ALP but normal activity of ALT, suggesting cholestasis rather than hepatic necrosis. Another study[8] in rats does not confirm this finding. A 2-year study[6,9] in which 8 male and 8 female Beagles were fed a diet containing up to 20% (approx 12 g/kg of body weight/d) xylitol also failed to detect any serious liver lesions. Although the dose was similar to those reported here, the amount of xylitol in the diet was slowly increased to allow for accommodation. Mild intermittent increases in activity of ALT were detected in individuals in the 20% group. This was thought to be caused by glycogen accumulation in periportal hepatocytes that led to a slight swelling of the cells and ALT leakage because of altered membrane permeability. No evidence of hepatic necrosis was seen.

Although no evidence of hepatic necrosis has been seen with experimental oral xylitol administration, substantial hepatic changes have been detected with IV xylitol administration in various species. In 1 study,[10] rabbits receiving an infusion of concentrated xylitol solution developed high bilirubin concentration and high activities of AST, ALT, LDH, and creatine kinase. Some of the toxicity was attributed to the solution's hyperosmolarity. However, rabbits administered lower-concentration xylitol solutions also developed high activities of liver enzymes. Histologic evaluation of 1 rabbit revealed hepatocellular damage. Another study[10] detected coagulation necrosis of the liver in rats infused with high doses of xylitol. In a study[11] of 2 human volunteers, a 10% xylitol solution (4.4 g/kg/d) was administered IV. The trial was terminated after 3 days because both subjects complained of right upper quadrant pain, nausea, headache, and vertigo. Both

volunteers developed jaundice, high concentrations of bilirubin, and high activities of ALT, AST, ALP, and LDH. These values returned to reference ranges, although the bilirubin concentration and LDH activity remained high for approximately 9 days. In 1 study[12] of total parenteral nutrition in dogs that used xylitol as an energy source, substantial dose-related increases in serum activities of ALT and ALP occurred. The effects were reversible with discontinuation of the infusion. No histologic evaluations were performed. However, increases in activities of ALT and ALP also occurred with infusion of concentrated glucose and sorbitol solutions, suggesting that the effect may not be xylitol-specific.[12]

The mechanism of xylitol-induced hepatic necrosis in dogs is not known. The authors propose 2 possible mechanisms. During hepatic metabolism of xylitol and its metabolites, phosphorylated intermediates are produced.[13] In vitro studies[14,15] of hepatic metabolism of xylitol in rats indicate that these intermediates can deplete cellular ATP, ADP, and inorganic phosphorus reserves. Adenosine triphosphate is needed to maintain normal cellular functions such as protein synthesis and membrane integrity. Therefore, xylitol-induced hepatic necrosis in dogs might result from prolonged ATP depletion and consequent cellular necrosis.[14] A second possible mechanism involves reactive oxygen species. Xylitol metabolism results in high concentrations of cellular nicotinamide adenine dinucleotide.[16] Mitochondrial metabolism of nicotinamide adenine dinucleotide can produce reactive oxygen species,[16] which can damage cellular membranes and macromolecules. This damage can decrease the viability of hepatocytes.[16] Either proposed mechanism, or both together, could be responsible for xylitol-induced hepatic necrosis in dogs.

Coagulopathy is a common finding in acute hepatic failure and results from a combination of factors. Acute loss of > 70% of liver mass can result in impaired production of clotting factors, and severe hepatic necrosis may be associated with disseminated intravascular coagulation; thrombocytopenia can worsen the hemorrhage. The high concentrations of fibrin degradation products and D-dimers detected in 2 of the dogs of this report may have been caused by disseminated intravascular coagulation, inability of the liver to clear these factors, or both.[17]

In this report, xylitol doses associated with hepatic failure ranged from 1.4 to 2.0 g/kg (0.6 to 0.9 g/lb) to 16 g/kg (7.3 g/lb). In our experience, ingested xylitol at a dose of 0.15 g/kg (0.07 g/lb) has caused hypoglycemia in dogs. Survival in the dogs in this report did not appear to correlate with dose. The dog that ingested the highest dose survived, whereas the dog that ingested the lowest dose died in approximately 2 days.

Prior to this report, the time to onset of clinical signs after xylitol ingestion was considered short, usually within 30 minutes to an hour.[4] However, 6 of the dogs in this report did not have early signs of hypoglycemia, such as weakness, ataxia, or seizures. Instead, they had signs associated with acute hepatic failure approximately 9 to 72 hours after ingestion. The reason that these 6 dogs did not initially develop hypoglycemia was not apparent.

The histopathologic changes in the 3 dogs that were necropsied were considered consistent with acute toxic hepatic necrosis. Cholangiohepatitis in one dog and lymphoplasmacytic enteritis in another likely represented preexisting conditions. Whether these conditions predisposed the dogs to hepatic necrosis associated with xylitol toxicosis was not known.

Two dogs had high serum activities of ALT, but samples obtained a few hours later and analyzed by a different laboratory and instrument yielded results within reference range. Because both dogs had histologic evidence of severe hepatic necrosis, we attributed the discrepancy to error on the part of the second laboratory. Another apparent anomaly was the initial decrease in the first dog's BUN concentration despite high serum creatinine concentration. This anomaly may have resulted from the osmotic pressure caused by xylitol in the gastrointestinal tract. Such osmotic pressure is a potential effect of all sugar alcohols.[6] The BUN later returned to reference range in this dog.

Although hypoglycemia is expected shortly after xylitol ingestion, 3 dogs did not become hypoglycemic until 24 to 48 hours after ingestion. This delay in hypoglycemia may have been a consequence of ongoing hepatic failure rather than xylitol's stimulation of insulin secretion.

Although the first dog of this report was initially hypophosphatemic, the dog later became markedly hyperphosphatemic. Initial hypophosphatemia may have been related to respiratory alkalosis associated with tachypnea[18]; for instance, tachypnea may have occurred during an unwitnessed seizure secondary to severe hypoglycemia. Alternatively, hypophosphatemia may be a direct effect of liver failure. In humans, hypophosphatemia is a common finding early in the course of acetaminophen-induced hepatic toxicosis, although the cause is unknown.[19] Hyperphosphatemia is also a common finding in humans with acute hepatic failure and is possibly associated with release of inorganic phosphate from the liver because of cellular necrosis, decreased uptake of phosphate by the liver,[20] or concurrent renal impairment.[19] In humans, hyperphosphatemia in acute hepatic failure is associated with increased mortality rate, whereas hypophosphatemia is associated with increased survival rate.[19–21] In this case report, 4 of the 5 dogs that died or were euthanatized were hyperphosphatemic; a phosphorus value was not available for the fifth dog.

Other than xylitol, potential toxicologic causes of acute hepatic necrosis in dogs include ingestion of acetaminophen, Sago palm (*Cycad* spp), *Amanita phalloides* and similar hepatotoxic mushrooms, aflatoxins, iron, or blue-green algae.[22,23] There is no evidence that the dogs in this report were exposed to any of these toxicants. Other causes of acute hepatic necrosis include infectious agents (such as canine hepatitis virus, leptospires, mycotic organisms, and toxoplasma organisms), trauma, and heatstroke.[19]

Each year, the number of US products containing xylitol and the number of reports to the APCC of canine xylitol exposure have increased. The number of reported exposures was 3 in 2002, 20 in 2003, 82 in 2004, and 193 in 2005. During the first half of 2006,

the APCC received 138 reports of xylitol ingestion. Apart from the increased availability of products containing xylitol, the increase might be attributable to increased awareness among clinicians and the public of xylitol toxicosis in dogs.

Clinicians should treat xylitol ingestion aggressively to avoid possible life-threatening consequences for the patient. If possible, any dog that ingests a substantial amount of xylitol (> 0.1 g/kg [0.045 g/lb]) should be treated. However, because of risk of aspiration, emesis should not be induced if signs of hypoglycemia have already developed (hypoglycemia may develop within 30 minutes of ingestion).[4] Results of an in vitro study[24] suggest that activated charcoal may be of limited benefit because its adsorption of xylitol is unreliable. Blood glucose concentration should be monitored, and dextrose should be administered IV, especially if the amount of ingested xylitol is large. It may be prudent to administer dextrose even in dogs in which hypoglycemia has not yet developed. Liver enzyme values, total bilirubin concentration, platelet counts, and coagulation variables should be monitored for 48 to 72 hours or more after ingestion. If signs of coagulopathy develop, plasma or whole-blood transfusions may be helpful. Hepatic protectants such as n-acetylcysteine, S-adenosyl-L-methionine, and silybin might be beneficial, especially if they are administered early in the course of the toxicosis. Delaying treatment, even in a dog with no clinical signs, may increase the risk of fatal hepatic necrosis.

a. Nutballz Energy Cookies, Spring Foods Inc, Boulder, Co.
b. Carefree Koolerz Sugar Free Gum, Hershey Food Corp, Hershey, Pa.
c. Atkins Sugar-Free gum, Atkins Nutritionals Inc, Ronkonkoma, NY.

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