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TOXICOLOGY OBSERVATION

Acute Hepatic Failure in a Dog after Xylitol Ingestion

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Abstract Xylitol is a five-carbon sugar alcohol produced from natural resources frequently used as a sugar substitute for humans. We report the development and successful treatment of acute hepatic failure and coagulopathy in a dog after xylitol ingestion. A 9-year-old 4.95 kg (10.9 lb) neutered male Chihuahua was evaluated at a veterinary clinic for vomiting after ingesting 224 g (45 g/kg, 20.5 g/lb) of granulated xylitol. Hypoglycemia developed within 1–2 h, elevated liver values, suggesting the development of acute hepatic failure, within 12 h and coagulopathy less than 24 h after ingestion. Treatment included maropitant, intravenous dextrose, phytonadione, metronidazole, and fresh frozen plasma. *N*-acetylcysteine (NAC) and *S*-adensoyl-L-methionine (SAMe) provided hepatic detoxification and support. The dog survived and liver values returned to normal within 1 month post ingestion. No adverse effects to hepatic function have been identified 2 years after acute xylitol toxicity. This paper is one of the few reports of successful management of a dog with hypoglycemia, hepatic failure, and coagulopathy caused by xylitol toxicity. To date, this is the highest published xylitol dose survived by a dog, as well as the only reported case that documents laboratory changes throughout the course of toxicity and includes normal hepatic indices for 7 months following xylitol toxicity. The rapidly expanding use of xylitol in a variety of products intended for human consumption has led to a rise in xylitol toxicity cases reported in dogs, and clinicians should be aware that more dogs may potentially be exposed and develop similar manifestations.

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Introduction

Xylitol, a pentahydroxy sugar alcohol, with a sweetness index similar to sucrose [1], was first discovered by a German scientist named Emil Fisher in 1891 [2]. It occurs naturally in many fruits and vegetables, such as strawberries, raspberries, plums, and lettuce [1], and is manufactured by extracting xylan (a polysaccharide found in hardwoods), hydrolyzing xylan to monosaccharide units (D-xylose), and then hydrogenating the D-xylose to produce xylitol [3]. A sucrose shortage during World War II caused an increased production and use of xylitol. Its popularity was short lived, however, and use decreased after the war when sucrose was once more available and the need for extensive purification made continued production costly and time consuming [1]. The use of xylitol resurfaced in the 1970s when it was found not only to be an excellent sweetener, but also have numerous health benefits. Today, xylitol is also being produced using resources such as corncob remnants from ethanol plants [4].

Xylitol has been shown to be anticariogenic and has antimicrobial properties against common oral bacteria, which make it a popular addition to gums and candies [1, 4]. It has a low glycemic index and requires few carbohydrates for metabolism, as seen with its lower calorific value, 2.4 kcal/g compared with 4.0 kcal/g for sucrose, making it an ideal sweetener for diabetics [5]. However, xylitol use is not limited to its effectiveness as a sweetener. Research continues to show the unique advantages of xylitol to human health. Recent studies in humans have shown a likely benefit in chewing xylitol containing gum to help restore the bowel motility postoperatively [6]. Due to its humectant properties, xylitol is used in

many non-food items, including deodorants and skin gels. Additionally, a recent study showed promising use in the protection against anti-microbial resistance due to its anti-adherence properties [7]. These benefits have led to the expansion of xylitol use over the past several decades.

As the use of xylitol in products for human consumption grows so does the potential for exposure and resulting toxicity in dogs. Xylitol is a very safe sugar substitute in humans and many other animals; however, the toxicity to dogs is high, where hypoglycemia may be seen with ingestions of 0.1 g/kg body weight and hepatic necrosis at 0.5 g/kg [2]. Inadvertent ingestion of xylitol containing gum and candies has been common causes of canine toxicity for over 10 years. The use of human prescription medications in dogs may pose a toxicity risk as xylitol is frequently used to increase the palatability, particularly those that are in a liquid or chewable form. More recently, the addition of xylitol to sugar-free peanut butter products has become a topic of concern in the veterinary field, as many dog owners use peanut butter as treats or an aid in medication administration. The increased use of xylitol to enhance the palatability and provide health benefits in human products has resulted in a need for heightened awareness of xylitol toxicity among veterinary professionals. We report the development and successful treatment of hypoglycemia, acute hepatic failure, and secondary coagulopathy in a dog after large xylitol ingestion.

Case Report

A 9-year-old 4.95 kg (10.9-lb) neutered male Chihuahua was evaluated for persistent vomiting at a veterinary clinic after ingestion of 224 g granulated xylitol 1 h prior to presentation. The ingested xylitol dose was calculated to be 45 g/kg (20.5 g/lb). Physical examination (PE) revealed no abnormalities, other than abdominal discomfort. Initial diagnostics included complete blood count (CBC) and serum chemistries. Laboratory findings revealed normal complete blood count values, hypoglycemia at 60 mg/dL, mild hypokalemia at 3.1 mmol/L, mild increase in serum alanine transferase (ALT) at 203 U/L, normal serum alkaline phosphatase (ALP) at 11 U/L, and increased total bilirubin (T.bil) 0.7 mg/dL (Table 1). Therapy included maropitant 1 mg/kg subcutaneously (SQ) q 24 h (H), metronidazole 25 mg/kg oral (PO) q 12 H, and *S*-adenosyl-L-methionine (SAMe) 18 mg/kg PO q 24 H. Intravenous Lactated ringer's solution with 5 % dextrose was administered at 30 mL/h (6 mL/kg/h).

Once stabilized, the dog was transferred to a referral facility for further care. *N*-acetylcysteine (NAC) 121 mg/kg PO to load, followed by 60 mg/kg PO q 4 H, was added to the treatment plan from the referring facility. Intravenous fluid therapy was continued with 5 % dextrose in Plasmalyte at 28 mL/h (5.6 mL/kg/h). Serum chemistries obtained 12 h post ingestion showed increasing concentrations of ALT at 2235 U/L and serum gamma-glutamyl transpeptidase (GGT) at 14 U/L (see Table 1). Due to elevations in hepatic indices, coagulation factors were assessed. Results showed the prothrombin time (PT) at 19 (11–17) s and partial thromboplastin time (PTT) at 92 (72–102) s.

By 24 h post ingestion, coagulopathy had developed with a PT of 62 s and PTT of 125 s. Other factors for assessing clotting such as activated clotting time (ACT) and fibrinogen were not evaluated. Hepatic enzymes remained elevated with ALT 2004 U/L, GGT 15 U/L, and T.bil 1.1 mg/kg. Fresh frozen plasma (FFP) was administered at 24 mL/kg IV over 4 h. Mild facial edema developed during administration, which resolved with administration of 12.5 mg (2.5 mg/kg) diphenhydramine intramuscularly (IM). Prothrombin time and PTT 3 h post FFP administration were within the normal range at 16 and 95 s, respectively. Within 12 h post FFP administration, it was noted that the dog had developed ecchymotic hemorrhage along venipuncture sites.

Over the next 36 h, hepatic indices improved with the exception of a transient increase in GGT and T.bil, but remained well above normal reference values (Table 1). Medical therapy was continued as previously described with NAC, maropitant, 5 % dextrose in Plasmalyte, metronidazole, and SAMe. Phytonadione (2.5 mg/kg PO q 12 h) was initiated at 72 h post ingestion. The dog's clinical status improved with a bright attitude, good appetite, and no additional signs of hemorrhage. *N*-acetylcysteine was discontinued after a total of 17 doses. Four days post ingestion, maropitant was discontinued, and dextrose supplementation decreased to 2.5 % for 12 h and discontinued that evening as euglycemia was maintained. All clinical signs were resolved, the dog was readily eating and drinking, and hepatic indices continued to improve (Table 1).

The dog was discharged 5 days post ingestion with phytonadione (2.5 mg/kg PO q 12 h), metronidazole (25 mg/kg PO q 12 h × 8 days), and SAMe (18 mg/kg PO q 24 h × 30 days). Hepatic values were repeated at 1, 3, and 7 months after ingestion and showed all hepatic indices within normal parameters (Table 2). The dog has continued to be healthy for the last 2 years and shows no evidence of residual damage from hepatotoxic insult.

Discussion

The pharmacokinetics of xylitol are well described in humans and less so in animals. It is incompletely absorbed in the stomach and upper gastrointestinal tract by an amount of 20–30 % less than that of glucose [1]. Absorption and peak plasma levels occur within 3–4 h in humans, yet, peak plasma levels are rapidly reached within 30 min in dogs [8]. Xylitol is primarily metabolized in the liver (70–80 %) by oxidation to

Table 1 Laboratory findings

Parameter	Reference range	Time interval (approximate)							
		1.5 h***	12 h	24 h	36 h	48 h	60 h	72 h***	4 days***
Potassium	3.5–5.8 mmol/L	3.1	4.5	3.1	3.9	4.9	5.3	3.6	3.9
Chloride	109–122 mmol/L	–	119	132	119	111	115	–	–
Glucose	60–110 mg/dL	60	116*	138*	107*	216*	110*	115*	128*
BUN	7–27 mg/dL	13	5	9	8	10	12	16	–
ALT	10–118 U/L	203	2235	2004	1355	753	939	670	418
GGT	0–7 U/L	–	14	15	15	20	14	–	–
ALP	23–212 U/L	11	71	46	101	74	97	59	–
T. Bilirubin	0.1–0.6 mg/dL	0.7	0.5	1.1	2.0	2.0	1.2	1.0	0.8
PT	11–17 s	–	19	62	16**	14	14	–	–
PTT	72–102 s	–	92	125	95**	94	75	–	–

Unless otherwise noted, testing was performed on IDEXX catalyst analyzer

*Blood glucose values while receiving 2.5–5 % dextrose supplementation

**Three hours post fresh frozen plasma transfusion values

***Performed on Abaxis VS2 analyzer

−Denotes values were not obtained

D-xylulose. D-xylulose is phosphorylated to an intermediate in the pentose phosphate pathway which is then converted to glyceraldehyde-6-phosphate or fructose-6-phosphate, ultimately forming glucose, glycogen, or lactate [4]. The majority of xylitol is converted to glucose, with a small amount being converted to lactate [4]. The remainder of xylitol (20–30 %) is metabolized by lungs, kidneys, myocardium, fat stores, and erythrocytes, where they are then converted into carbon dioxide and water through carbohydrate metabolism [1].

While xylitol use has proven to be quite safe in humans, rhesus monkeys, horses, and rats, significant toxicity concerns exist in the dog [8]. In humans, xylitol causes little to no insulinotropic effects and ingesting >130 g/day results only in diarrhea [2], whereas in dogs, xylitol stimulates pancreatic insulin secretion leading to profound hypoglycemia [9]. Dogs develop a dose-dependent increase in plasma insulin concentration after ingesting xylitol [4]. The insulin release is 2.5–7 times greater than that seen with the equivalent amount of ingested glucose [4]. Plasma insulin concentrations were not evaluated in this case due to cost and difficulty in obtaining in veterinary medicine. The LD_{50}, used to assess a substance's acute toxicity, varies considerably from species to species. The LD_{50} in mice is >20 g/kg [3]. While the LD_{50} in dogs ingesting xylitol has not yet been established, a report in rabbits showed an LD_{50} to be 4–6 g/kg [10]. Established LD_{50} doses in other susceptible species, such as the cow, baboon, and goat, have not been identified [11].

Table 2 Laboratory findings

Parameter	Reference range	1 month	3 months	7 months
ALT	12–118 U/L	52	79	64
GGT	1–12 U/L	<5	12	-
ALP	20–150 U/L	39	135	35
T. Bilirubin	0.1–0.3 mg/dL	0.1	0.1	0.3

Testing performed on Abaxis VS2 analyzer

−Denotes values were not obtained

In dogs, vomiting due to the development of hypoglycemia 30–60 min post ingestion is commonly seen as the first sign of xylitol toxicosis, followed by lethargy, weakness, and ataxia [2]. Elevations of serum hepatic enzyme concentrations may occur as early as a few hours after ingestion or be delayed by 24–48 h. Coagulopathies that develop in dogs with xylitol toxicosis are likely secondary to acute hepatic failure, disseminated intravascular coagulopathy, or both [8]. Two previous reports described the onset of liver failure in dogs after ingestion [3, 12]. One single case report [12] showed full recovery, while a second report showed three out of eight dogs likely recovering [3]. More recently, a retrospective report of 192 cases with xylitol toxicity showed no reports of hepatic failure as a sequela [4].

Even though an LD_{50} for xylitol ingestion in dogs has not been established, toxicity has been reported with hypoglycemia at 0.1 g/kg and hepatic necrosis possible at 0.5 g/kg [8]. The dog in this case ingested a massive dose of 45 g/kg, almost 100 times the dose where hepatic necrosis is possible and three times the highest dose where hepatic necrosis has been previously successfully treated and reported, yet fatal in two others [3]. Early clinical

signs and laboratory values followed the expected scenario with vomiting and hypoglycemia occurring less than 1 hour after ingestion. Maropitant, a neurokinin-1 receptor antagonist, was used successfully to control emesis, and intravenous dextrose was successful for the treatment and prevention of hypoglycemia. Mild increases in hepatic indices were present less than 2 hours of ingestion, with significant elevations at 12 h. Metronidazole, an antibiotic effective against obligate anaerobes including *Clostridium sp.*, a common bacteria present in hepatic infections, was administered prophylactically. Together, these therapies effectively controlled the early clinical signs in this dog.

Elevations in ALT at early onset are consistent with hepatocellular injury, as soluble cytosolic enzymes are released from the liver due to altered cell membrane permeability from sub lethal injury or necrosis. In dogs, ALT levels rise within 12 h of toxic insult and peak in 1 to 2 days. The decline of ALT by at least 50 % within one half-life, approximately 60 h, is a favorable sign in dogs with acute hepatic injury. The marked elevation with subsequent decline over 72 h, as seen in this case, is consistent with acute hepatocellular damage. The fact that the dog maintained normal ALP values throughout its toxicosis not a surprising finding as ALP is not readily released from cells due to membrane permeability and ALP enzymes are not specific to the liver. Elevation in GGT concentrations may occur with hepatic injury, however, has a lower specificity than ALT. Total bilirubin elevations occur due to hemolysis, hepatocellular disease, and extrahepatic obstruction of bile flow. In relation to other hepatic indices and ingestion history, T.bil elevations for this dog are likely secondary to hepatic disease with reduced functional liver mass due to necrosis. Liver biopsies, the preferred method for confirming a diagnosis, were not pursued in this dog as it responded well to therapy and indices declined appropriately. Elevations in PT and PTT generally preclude a liver biopsy and would be contraindicated in animals with coagulopathy.

The cause of hepatic necrosis in canine xylitol toxicosis is unknown, but two theories have been proposed. One thought is that depletion of adenosine triphosphate (ATP) may result in the inability of the liver cells to perform necessary cellular functions, including protein synthesis and maintenance of membrane integrity, which result in cellular necrosis [3]. Another proposed mechanism is that the metabolism of xylitol results in high concentrations of cellular nicotinamide adenine dinucleotide, which produces reactive oxygen species that can damage cellular membranes and macromolecules, leading to decreased viability of hepatocytes [3].

Glutathione is essential in cell detoxification and many metabolic processes. *N*-acetylcysteine is recommended for hepatic failure secondary to many drug-induced problems including xylitol toxicosis. In addition to its mucolytic properties, it is effective at restoring glutathione synthesis and reducing oxidative stress in the liver. *S*-adensoyl-L-methionine is present in three major biochemical pathways important to the liver including transmethylation, transsulfuration, and aminopropylation. Through these pathways, SAMe plays a role in liver mass regeneration, cell membrane structure, fluidity and function, and cell detoxification and is converted to glutathione. The liver normally produces SAMe, however, in a diseased state endogenous SAMe conversion is decreased, thus the administration of exogenous SAMe may increase liver glutathione levels and prevent its depletion. Indications of altered liver function contributed to its use in this dog.

Coagulopathy is a common sequela to hepatic disease in dogs leading to an increase in PT and PTT, as evident in this case. All coagulation factors, with the exception of factor VIII, are synthesized in the liver which is the site for vitamin K-dependent activation of factors II, VII, IX, and X. Vitamin K deficiency may be seen due to altered enterohepatic circulation of bile acids, leading to malabsorption. Fresh frozen plasma treatment was successful in restoring PT and PTT values and was chosen as it provides all of the coagulation factors in their active form. The presence of ecchymotic hemorrhages in this dog suggested that phytonadione be administered to allow for the production of factors II, VII, IX, and X while hepatic injury was repaired. Fibrinogen and activated clotting times may be used to evaluate the clotting function; however, PT and PTT is most frequently used in dogs due to its availability in practice and cost effectiveness.

In the dog, xylitol ingestion causes hypoglycemia, acute hepatic failure, and in rare cases, coagulopathies. There is no antidote for xylitol toxicosis, and general treatment guidelines include decreasing absorption, treating emesis, stabilizing blood glucose, protecting the liver, addressing coagulopathies, and providing further care as needed. Due to low binding properties, activated charcoal is not typically used [12]. Monitoring blood glucose closely and providing dextrose supplementation when needed is critical in the early stages of management for xylitol toxicosis. The use of hepatic protectants such as SAMe and NAC, monitoring hepatic parameters for a minimum of 2–3 days, and providing supportive care are necessary for a positive outcome in overdose situations. While xylitol ingestion is potentially life-threatening in dogs, this report has shown that acute hepatic failure as a result of xylitol toxicosis may be successfully treated with aggressive therapy. As the use of xylitol continues to expand, it is important for both human and animal medical professionals to be vigilant about use, carefully assess product labels, and provide early and appropriate care.

Compliance with Ethical Standards

Conflicts of Interest None

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