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Xylitol: A Sweet Poison For Dogs

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Summary

Xylitol is a 5-carbon sugar alcohol commonly used as an artificial sweetener leading to life-threatening situation particularly in dogs. Xylitol mainly causes hepatic toxicosis and hypoglycaemia in dogs. Therefore, any severe hypoglycaemic condition should be diagnosed and treated at the earliest. Creating awareness among the pet owners regarding the foodstuffs that should not be fed to dogs can keep them healthy and prevent several cases of poisoning.

Introduction

The companionship between dogs and humans in recent times has increased the number of food-related poisoning cases in dogs. Foods perfectly suited for human consumption can be toxic to their pet dogs. Xylitol poisoning is one of the alarming concerns due to the feeding of human foods to dogs. These poisoning incidences occur mainly due to a lack of public awareness associated with serious health issues in dogs. Even these food products are widely available at home so the dogs have easy and accidental access to them.

Xylitol is a 5-carbon sugar alcohol that is a metabolic intermediate of the glucuronic acid pathway. It was discovered by Emil Fisher in 1891 and used for the first-time during World War II as a sugar substitute. The sugar corresponding to xylitol is xylose. Commercially, most xylitol is extracted from corn fibre or birch trees *(Betula pendula)*. It is extensively used as an ingredient in candies and gum products and for baking.

Xylitol has a low glycemic index therefore used as a sugar substitute in diabetic patients and also tastes similar to sucrose. In recent years, increased use of xylitol as a sweetener has led to an enhanced risk of exposure to pets. Dogs are at high risk of developing severe, life-threatening clinical signs. In addition to its usage as a sugar substitute, it shows anti-cariogenic effects.

Sources

Naturally, xylitol is found in berries, plums, mushrooms, lettuce, corn, oats, trees, and some other fruits. Primarily it is used as an artificial sweetener in many products, including sugar-free gum, candy, bread, cookies, and other baked goods. It is also found in various nutritional supplements such as chewing gum, mint candy, lollipop, some prescription medicines, various vitamins (multivitamin tablets, iron, vitamin D chewable tablets, etc.), coenzyme Q10, 5-hydroxytryptophan, chocolate, pudding, fruit

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preserves, jellies, jelly beans, beverage powders, toothpaste, mouth lozenges, moisturizing mouth sprays and mouthwash solutions.

Because of its antibacterial activity and palatability, xylitol is also included in a variety of medical and dental care products. An additional concern is that the use of xylitol is not just confined to products intended for human use. Xylitol is also an ingredient in drinking water additives developed to help maintain dog and cat dental health.

Toxicity

Doses, as low as 0.03 g/kg, results in hypoglycaemia in this species. Ingestion of xylitol (@ 0.15 g/kg) leads to profound hypoglycaemia caused by stimulation of pancreatic insulin secretion. It causes 2.5 to 7-fold increase in insulin secretion in dogs compared with an equal amount of glucose. In addition to the hypoglycaemic effects, elevated hepatic enzymes or liver failure also occur 8-12 hours post-xylitol ingestion. A cup of xylitol powder contains 192g of xylitol and chewing gums have approximately 1g/stick. Doses more than 0.5 g/kg are associated with hepatotoxicity. LD50 of xylitol is not yet determined for dogs but toxicosis is reported with 0.1 g/kg leading to hypoglycaemia and at dose 0.5 g/kg causes hepatic necrosis. Due to the development of hypoglycaemia, vomiting occurs within 30-60 minutes after a meal which is the first sign of toxicosis, followed by weakness, ataxia and lethargy.

Toxicokinetics

In dogs, 1 or 4 g/kg of oral administration of xylitol elevates plasma insulin concentrations within 20 minutes which reaches the peak at 40 minutes. Approximately 80% of xylitol is metabolized by liver where it is rapidly oxidized to D-xylulose, then to glucose, glycogen, and lactate via the pentose-phosphate pathway. Remaining 20-30% xylitol is metabolized by the fat stores, erythrocytes, myocardium, kidneys and lungs, where it is converted into water and carbon dioxide through carbohydrate metabolism.

Xylitol is a potent stimulator of insulin in dogs, leading to hypoglycaemia. It directly stimulates pancreatic β-cells to secrete insulin in a dose-dependent manner. The increased insulin level then causes significant decreases in blood glucose levels. Hypoglycaemia alters the red blood cell membranes, instigating break down and release of bilirubin.

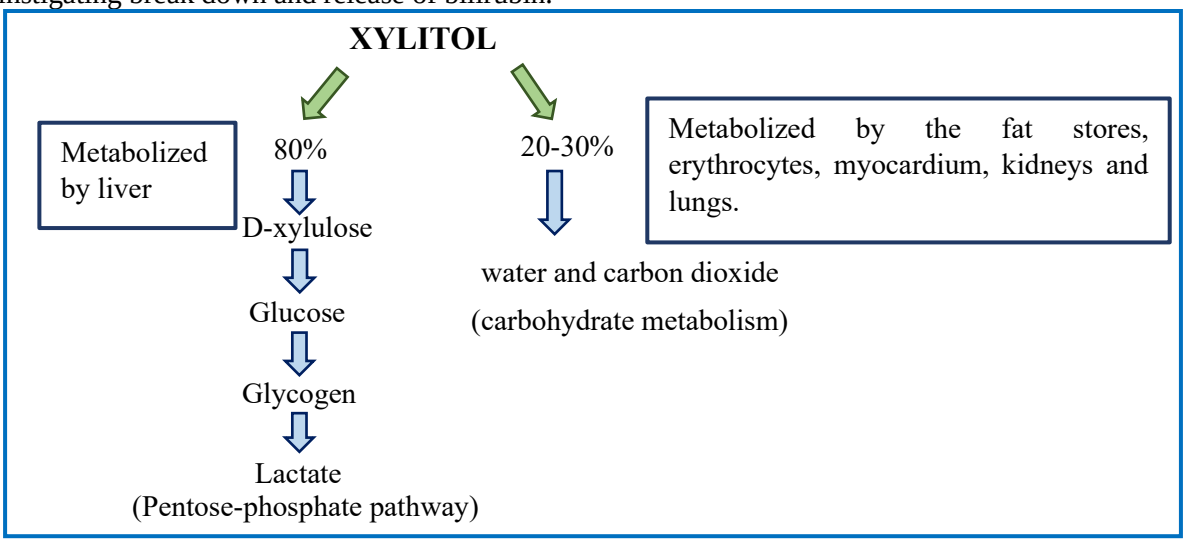

Figure 1. Metabolism of xylitol

Mechanism of Toxicity

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Xylitol mainly causes hepatic toxicosis and hypoglycaemia in dogs. However, the exact mechanism of toxicity is unknown. Similar to glucose, xylitol also stimulates insulin secretion, but this insulin-secreting effect i.e. hyperinsulinemia is extremely stronger in the dog causing profound hypoglycaemia by stimulating the synthesis and secretion of insulin. The toxic mechanism of action of xylitol-associated hepatic damage is thought to be related either to depletion of adenosine triphosphate (ATP) or the generation of damaging reactive oxygen species or both.

Xylitol is mainly metabolized in the liver and this metabolic process requires ATP. When large amounts of xylitol reach into the liver for detoxification, it results in high concentrations of cellular nicotinamide adenine dinucleotide (NAD+) that produces reactive oxygen species (ROS). NAD+ is an important cofactor acting as an electron carrier which is reduced to NADH by glycolysis in the cytoplasm. Cytosolic NADH directs the osmotic-chemical synthesis of ATP and is transported to the mitochondria. To prevent oxidative stress damage and to alleviate and eliminate ROS against cell homeostasis, mitochondria have their enzymatic mechanism which works as an antioxidant defence system. If the level of ROS exceeds the antioxidant defence system, the mitochondrial inner membrane permeability is lost resulting in apoptosis. Thus, excessive xylitol consumption causes ATP depletion in hepatocytes leading to excessive ROS generation causing hepatocyte necrosis. There is leakage of soluble cytosolic enzymes alanine transaminase (ALT) and aspartate transaminase (AST) from the liver due to alteration of cell membrane permeability. In some dogs, hyperbilirubinemia and coagulopathies also developed suggestive of severe acute hepatic necrosis. Coagulopathy results from impaired production of clotting factors due to loss of hepatic mass and severe hepatic necrosis.

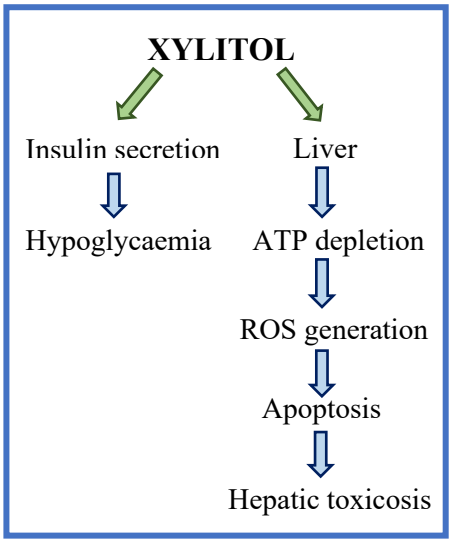

Figure 2. Mechanism of xylitol toxicity

Clinical Signs

In dogs, the clinical signs of xylitol intoxication may be associated to hypoglycemia or hepatopathy or both. The dose-dependent effects on insulin secretion include vomiting, lethargy, weakness, ataxia, and seizures. The neurologic changes are commonly observed within 30-60 minutes of ingestion. Ingestion of 0.15 g/kg xylitol leads to hypoglycaemia and 1.4 g/kg related to hepatic failure.

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With the developing hepatopathy, lethargy, icterus, vomiting, and coagulopathic signs, such as petechiae, ecchymoses, and gastrointestinal haemorrhages, may be observed.

Factors affecting xylitol toxicity

The main factors that govern the toxicity of xylitol are as follows:

- Species: Cats, rabbits, ferrets, and horses do not develop hypoglycaemia or liver failure after ingestion of xylitol. Dogs seem to be the most sensitive species to xylitol poisoning.
- Size of animal: The size of the dog plays a vital role in the severity of the dog's response. Xylitol consumption has much more vulnerable effects in smaller dogs, because the toxin will have a greater effect on a small body mass.
- ROS level: If ROS level increases more than the antioxidant defence system, the mitochondrial membrane permeability is lost leading to apoptotic cell death. Xylitol intoxication augment the ROS level damaging the liver.
- NADPH level: Low NADPH level induce cellular damage due to increased ROS level.
- Low glutathione transferase activity produces more xylitol toxicity.

Diagnosis

Diagnosis can be done on the basis of history and hypoglycaemia condition in dogs suddenly after intake of xylitol-containing products. Xylitol toxicity should also be differentiated from other common causes of acute hepatic injury like other toxic (eg, acetaminophen, phalloidine), infectious (e.g. leptospirosis), or idiopathic causes etc.

Treatment and Management

Hospitalization for the monitoring of glucose, hepatic and coagulation abnormalities is recommended. There is no antidote for xylitol poisoning therefore the first step to manage xylitol toxicosis is to prevent further absorption by inducing vomiting. Emesis should be induced within 4-6 hours of xylitol ingestion early and in asymptomatic animals. Blood glucose levels and liver function should be monitored. If hypoglycemia develops, intravenous fluid therapy or intravenous dextrose (glucose) supplementation could be administered to correct glucose, potassium, and phosphorous levels. Hepatoprotectants like S-adenosylmethionine (SAMe), N-acetylcysteine, silymarin, along with antioxidants, vitamins C & E are included. The coagulopathy associated with hepatic injury might be due to decreased production of clotting factors, vitamin K1 deficiency, or disseminated intravascular coagulation so vitamin K1 can be supplemented in such cases. Antibiotics can also be recommended to prevent further infection.

Prevention

- The easiest way to prevent xylitol toxicosis is to keep the pets out of reach of xylitol-containing products.
- Sometimes, dog nut butter is given as a treat or as a vehicle for pills that might contain xylitol. So, check the label first to make sure it doesn't contain xylitol.
- Some veterinary products (e.g., gabapentin medication, mouthwashes) also contain small amounts of xylitol. If ingested in larger amounts than the prescribed dose, they can potentially result in toxicity.

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- Sharing of human food with pets should sometimes be avoided.
- Instead of using human toothpaste, use only pet toothpaste for pets.

Conclusion

The present article illuminates the exposure of dogs, to potentially harmful foodstuffs containing xylitol as a sweetener. As a toxicant, it affects hepatic functioning and causes severe hypoglycaemia which could be fatal if remain untreated or undiagnosed. Early recognition of clinical signs, proper history, and rapid appropriate therapy can greatly improve the prognosis in case of xylitol poisoning cases. Lack of awareness and the existence of large knowledge gaps in public regarding the hazards that certain foodstuffs may pose severe toxicities in dogs. Preventing exposure is the key to reduce the incidence of poisoning. Therefore, it is important to increase the knowledge of pet owners regarding the foodstuffs that should not be fed to dogs to keep them healthy and prevent several cases of poisoning.

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