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Acute Hepatic Failure Induced by Xylitol Toxicosis in Two Dogs

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Abstract : Two dogs were referred due to vomiting, depression and anorexia after ingestion of xylitol gum. Both dogs were presented with hepatic failure and one dog had concurrent renal failure. Aggressive supportive treatment was performed, but these dogs died. Necropsy of one dog revealed acute hepatic necrosis, severe renal damages, and hemoperitoneum. This case report demonstrates potential hazard of xylitol toxicity for dogs with clinicopathological and pathological findings.

Keywords **:** dog, hepatic failure, renal failure, xylitol

Introduction

Xylitol is one of a number of non-sugar sweeteners approved for use in foods and other items in many countries. Recently, the consumption of xylitol as a food supplement is increasing in Korea, especially in gums and candies. In dogs, unlike humans, xylitol causes a fast release of insulin, which results in hypoglycemia (1, 3-7). Furthermore, hepatic failure associated with xylitol ingestion was reported (4). This case report describes the lethal clinical manifestations after xylitol ingestion in two dogs and findings of postmortem examination.

Case Report

Case 1

A 4-year-old 9.5 kg castrated male Cocker Spaniel dog was presented with anorexia, depression, vomiting, and polyuria. This dog had ingested 45 pieces of sugar-free gum sweetened with the sugar-alcohol xylitol (*Xylitol*® gum) 3 days before presentation. It was estimated that xylitol was ingested at a dose of 4.73 g xylitol/kg body weight. The dog had not shown any signs of toxicity for two days, but 3 days after ingestion of xylitol sweetened gum, clinical signs were noted thereafter.

On physical examination, mild dehydration, hypothermia (37.2 °C), tachycardia, and icterus on oral mucosal membrane, ocular sclera, ear pinna, and ventral skin were noted. Abdominal pain on palpation was also detected. Mild leukocytosis and thrombocytopenia were shown on complete blood count (CBC) (Table 1). Serum biochemical profiles revealed mild azotemia, elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), gamma glutamyl transferase (GGT), hyperammonemia, hyperbilirubinemia, hyperphosphatemia and electrolytes imbalances (Table 2). Blood glucose concentration was in normal range. Radiographic examination showed gas-distended intestine and mild kidney enlargement. Bilateral renomegaly, hepatic parenchymal hyperechogenicity, and thickened gall bladder wall were observed on abdominal ultrasonographic examination. These findings strongly suspect acute renal and hepatic failure presumably due to xylitol intoxication based on the previous examination that was no remarkable.

On day 1, intravenous fluid therapy with 5 % dextrose Lactate Ringer's solution (LRS) supplemented with 20 mEq/L potassium chloride was initiated. Antiemetics (metoclopramide, 0.5 mg/kg, IV) and H2-receptor antagonist (cimetidine, 10 mg/kg, IV) were administered. Within several hours, clinical signs of the patient had been improved.

However, on day 2, mucosal membrane and skin surface became more icteric. Depression and continuous vomiting were also noted. Because of hyperglycemia, intravenous fluid therapy with 0.9 % NaCl with potassium supplement was instituted.

This dog exhibited hematemesis, melena, abdominal distension, tachypnea, petechia, ecchimosis and pale mucosal membrane on day 3 (Fig 1). Hematologic abnormalities were shown indicating moderate anemia and thrombocytopenia. Serum biochemical analysis revealed hypoproteinemia and

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Table 1. Complete blood count (CBC) results of the present cases

	Case 1				Case 2		
	Day 1	Day 2	Day 3	Day 4	Day 1	Day 3	Normal range
WBC (10^3/μl)	21.20	16.20	15.48	18.48	11.78	16.96	6.0 – 17.0
Neutrophils (10^3/μl)	12.45	8.22	9.90	7.14	9.94	8.46	3.0 – 11.8
Lymphocytes (10^3/μl)	4.48	5.07	7.16	14.96	1.04	3.75	1.0 – 4.8
Monocytes (10^3/μl)	4.15	0.44	0.97	2.27	0.64	4.25	0.2 – 2.0
Eosinophils (10^3/μl)	0.11	0.01	0.01	0.02	0.15	0.47	0.1 – 1.3
Basophils (10^3/μl)	0.00	0.00	0.00	0.00	0.01	0.02	0.0 – 0.5
RBC (10^6/μl)	7.40	3.31	3.79	4.79	9.49	5.07	5.50 – 8.50
Hemoglobin (g/dl)	17.1	7.6	8.7	10.3	19.6	10.3	12.0 – 18.0
Hematocrit (%)	46.2	20.7	23.5	27.7	60.1	31.1	37.0 – 55.0
MCV (fl)	62.4	62.6	61.9	57.9	63.6	61.4	60.0 – 74.0
MCH (pg)	23.1	23.0	23.0	21.5	20.7	20.3	19.5 – 24.5
MCHC (g/dl)	37.0	36.7	37.0	37.2	32.6	33.1	31.0 – 36.0
Platelet (10^5/μl)	120	94	237	127	529	775	200 – 500

WBC; white blood cell, RBC; red blood cell, MCV; mean corpsular volume, MCH; mean corpsular hemoglobin, MCHC; mean corpsular hemoglobin concentration

Table 2. Serum biochemical profiles of the present cases

	Case 1				Case 2			
	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 3	Normal range
GLU	102	341	208	106	96	113	191	75-128 (mg/dl)
BUN	63.9	64.9	33.2	32.5	15			9.2-29.2 (mg/dl)
CRE	1.9	1.5	0.9	0.8				0.4-1.4 (mg/dl)
AST	>1000	>1000	867	750	227	>1000	>3000	17-44 (U/L)
ALT	>1000	>1000	>1000	>1000	>1000	>1000	793	17-78 (U/L)
ALP	561	556	56`	548	444	796	847	47-254 (U/L)
NH3	132	222	311	358				16-75 (mg/dl)
TBIL	4.1	4.6	10.7	12.0	30	2.6	3.2	0.1-0.5 (mg/dl)
Ca	10.1	9.2						9.3-12.1 (mg/dl)
P	9.9	3.6						1.9-5.0 (mg/dl)
TP	5.1		2.8	2.0	6.5			5.0-7.2 (g/dl)
ALB	3.0		1.7	1.5	3.8		1.8	2.6-4.0 (g/dl)
LDH	295		358	322				20-109 (U/L)
CPK	173		692	650				49-166 (U/L)
Tchol	160							111-312 (mg/dl)
TG	114							30-133 (mg/dl)
UA	0.1							0-2.0 (mg/dl)
GGT	41				206	31	21	5-14 (U/L)
Na	130	136	151	155	141		133	141-152 (mmol/L)
K	3.7	3.8	3.0	4.4	3.5		3.3	3.8-5.0 (mmol/L)
Cl	92	98	114	121	97		100	102-117 (mmolL)

ALB; albumin, ALP; alakaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BUN; blood urea nitrogen, CPK; creatine phosphokinase, CRE; creatinine, GGT; gamma glutamyl transferase, GLU; glucose, LDH; lactate dehydrogenase, NH3; ammonia, TBIL; total bilirubin, Tchol; total cholesterol, TG; triglyceride, TP; total protein, UA; uric acid

hypoalbuminemia. Besides, abdominal radiograph showed homogeneously increased radiodensity. Hemoabdomen or ascites were suspected from these findings. However, vitamin K (1 mg/kg, SC, q24h) injection and transfusion with whole blood were given to prevent coagulopathy. After blood transfusion, tachypnea of the patient was temporarily improved.

On day 4, abdominal distension and icterus became more severe and the patient showed lethargic condition. Despite

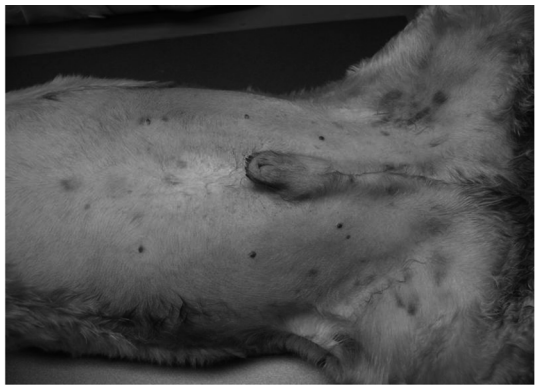

Fig 1. Photograph of the dog 1 in this case report. Mild abdominal distension, icterus, petechia, and ecchimosis were observed.

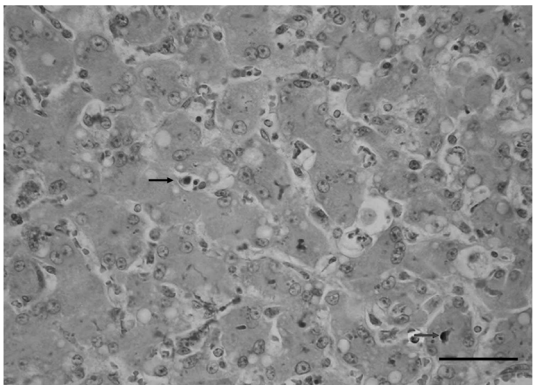

Fig 2. Microphotograph of the liver of dog 1. Hepatocellular degeneration and necrosis (arrow) were found. Bile plugging was also detected (arrow, bottom) (Hematoxylin and eosin stain. Scale bar = 50 μm).

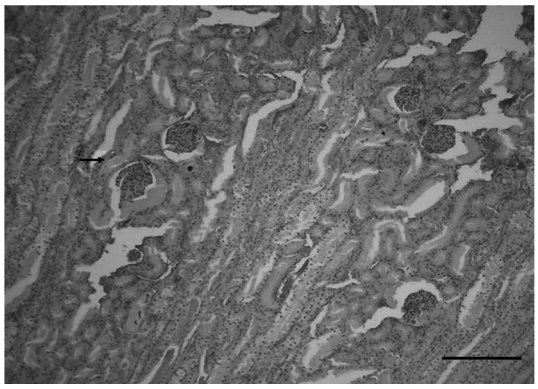

Fig 3. Microphotograph of the kidney of dog 1. Tubular degeneration and protein cast (arrow) were observed (Hematoxylin and eosin stain. Scale bar = 200 μm).

additional transfusion with whole blood and other supportive treatments, the patient died on day 5.

Necropsy was performed. Hemoperitoneum and hemorrhage of abdominal organs including liver and kidney were noted. On histopathologic examination, severe hepatocellular degeneration and necrosis with severe bile plugging in the bile canaliculi and mild biliary hyperplasia were noted (Fig 2). In addition, severe tubular degeneration, intratubular fragmented erythrocytes, severe bile accumulation, with protein casts were observed in the kidney (Fig 3). The lesions were appeared to be closely associated with massive hemolysis due to xylitol ingestion.

Case 2

A 5-year-old 8 kg castrated male Schnauzer dog was presented with vomiting, depression, anorexia. This dog had ingested 7 pieces of xylitol gum 1 day before presentation. The estimated dose of xylitol was 0.86 g xylitol/kg body weight. Dehydration and depression were observed on physical examination and polycythemia was detected on CBC (table 1). Serum biochemical profiles revealed elevated ALT, AST, ALP, GGT, bilirubin and electrolytes imbalances (table 2). Blood glucose concentration was in normal range. Hyperechoic hepatic parenchyma and thickened gall bladder wall were observed on abdominal ultrasonography. These findings suggested acute hepatic failure. Aggressive supportive therapy was initiated as case 1. Hematemesis and hemorrhagic diarrhea were noted on day 2. This dog eventually died on day 3. Unfortunately, necropsy was not performed.

Discussion

In dogs, xylitol administration caused a rapid and dose-dependent rise in insulin levels, with a concurrent hypoglycemia (1, 3-7). These results imply that immediate treatment is required in the cases of canine xylitol ingestion, especially hypoglycemic status. More importantly, induction of emesis immediately after ingestion can be crucial to treat the patient, since xylitol is absorbed very rapidly. However, emesis was not performed in both dogs since these dogs were presented after 1 to 3 days of xylitol ingestion. Previous study showed that activated charcoal may be beneficial to prevent further xylitol absorption (2).

Both dogs did not show hypoglycemia but severe hepatic failure. This discrepancy may be due to late presentation after xylitol ingestion. The cause of death in dog 1 can be related to severe hepatic failure after large quantities of xylitol (7.1 g xylitol/kg body weight of dog) resulting in death. In case 2, estimated xylitol dose (0.86 g xylitol/kg) was relatively smaller than that of case 1. This dose of case 2 was smaller than reported dose of 1.4 g/kg causing hepatic failure (4). However, it is unclear whether hypoglycemia had been existed. A previous report described rapid increase and decrease of plasma insulin level after xylitol infusion (7). Thus, it is presumably possible that hypoglycemia had been existed, but there was no hypoglycemia at the initial presentation.

Two possible mechanisms of xylitol-induced hepatotoxicity in dogs have been proposed. First, prolonged ATP depletion may lead to consequent cellular necrosis and, second,

cellular damages may be associated with reactive oxygen species (4).

Renal tubular necrosis in a case of xylitol ingestion was consistent with that of a previous report (4). However, xylitol effect on the renal tubules was not described in that report. The cause of renal failure in dog 1 can be associated with hemoprotein which is originated from acute hemolysis and decreased glomerular filtration rate due to a hypovolemia secondary to large volume of hemorrhage.

This case report indicates that xylitol could induce severe hepatic and renal failure in dogs not depending on the amount that they ingested. Thus, immediate, aggressive intensive care should be performed in the case of xylitol ingestion.

Acknowledgments

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References

1. Asano T, Greenberg BZ, Wittmers RV, Goetz FC. Xylitol, a partial homologue ot alpha-D-glucopyranose: potent stimulator of insulin release in dogs. Endocrinology 1977; 100: 339-345.
2. Cope RB. A screening study of xylitol binding in vitro to activated charcoal. Vet Hum Toxicol 2004; 46: 336-337.
3. Dunayer EK. Hypoglycemia following canine ingestion of xylitol-containing gum. Vet Hum Toxicol 2004; 46: 87-88.
4. 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.
5. Kuzuya T, Kajinuma H, Sando H, Hayashi M, Ide T, Kosaka K. Comparison of the early time courses of the release of insulin that follow injections of tetragastrin, tolbutamide, xylitol, and glucose into the pancreatic artery of dogs. Diabetes 1978; 27: 1189-1195.
6. Kuzuya T, Kanazawa Y, Kosaka K. Plasma insulin response to intravenously administered xylitol in dogs. Metabolism 1966; 15: 1149-1152.
7. Wilson RB, Martin JM. Plasma insulin concentrations in dogs and monkeys after xylitol, glucose or tolbutamide infusion. Diabetes 1970; 19: 17-22.