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Experimental acute toxicity of xylitol in dogs

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The Cases of xylitol poisoning in dogs are increasing as a result of ingestion of xylitol-containing products. Eighteen adult, clinically normal Pekingese dogs were orally dosed with 1 or 4 g/kg xylitol in aqueous solution. Blood samples were collected before and after dosing. Plasma insulin concentrations of both treated groups rose sharply from 20 min after xylitol dosing, peaking at 40 min. Hypoglycemia followed the increase in insulin concentration, with blood glucose values started to decrease 30 min after dosing. Other plasma biochemistry changes associated with xylitol administration were increased alanine aminotransferase and aspartate aminotransferase activities, hypophosphatemia, hypokalemia, and hypercalcemia. Plasma sodium and chloride concentrations remained normal. This study established a biochemical basis for diagnosis and treatment of xylitol poisoning in dogs.

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INTRODUCTION

Xylitol is used as a substitutive sweetener for diabetic patients (Brunzell, 1978; Levine, 1986) and in chewing gums for the prevention of dental caries especially in children (Honkala *et al.*, 2006). Dogs are sensitive to xylitol. Ingestion of xylitol-containing products such as chewing gums results in xylitol poisoning (Campbell & Bates, 2008). Xylitol poisoning in dogs is characterized by depression, vomiting, ataxia, and seizures. There have been many case reports of xylitol poisoning in dogs, but data on differential diagnosis and treatment of xylitol toxicity are lacking.

The aim of this study was to investigate clinical chemistry alterations in dogs with xylitol poisoning in order to provide a basis for the diagnosis and treatment of xylitol poisoning in clinical practice.

MATERIALS AND METHODS

Animals and treatment

Eighteen adult, clinically normal Pekingese dogs (9/sex, 3 ± 1 years of age; 7 ± 1 kg) were individually housed in metal cages, fed a commercial dog food (Adult meaty-bites, Pedigree, Beijing, China), and offered free access to tap water. They were walked in the morning and evening daily. The dogs were vaccinated against Canine Distemper virus, Adenovirus, Parvovirus, Parainfluenza virus and Rabies virus (Nobivac Vaccination, Intervet International B.V., Boxmeer, The Netherlands) at least 1 month before the experiment. The study was approved by the University Animal Ethics Committee.

The dogs were randomly divided into three groups (3/sex/-group). Base on the report (Kuzuya & Kanazawa, 1969), two groups were given 1 or 4 g/kg xylitol in distilled water, and one control group received distilled water (15 mL). The xylitol solution (15 mL) was orally administered to the animals as three portions of 5 mL by a syringe within a few minutes. Food was withheld for 12 h after xylitol dosing.

Clinical observation and sample collection

The dogs were observed for clinical signs before and after xylitol administration. Blood samples were collected from the cephalic vein or lateral saphenous vein 1 day and immediately before xylitol dosing and at 10, 20, 30, 40, and 50 min, and 1, 1.5, 2, 3, 4, 8, 12, 24, 72, 120, and 168 h after dosing. Blood samples (5 mL) were anticoagulated by sodium heparin (6,250 IU/mL) and centrifuged at 1000 ***g*** for 10 min (LD5-2A high-speed centrifuge, Beijing, China). Laboratory tests were performed as soon as possible on the day of blood collection. Otherwise, plasma was stored at −20 °C until analysis.

Laboratory tests

Serum concentrations of insulin, potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), chloride (Cl^-), and inorganic phosphorus (Pi) were determined using a Hitachi automated biochemical

analyzer (HITACHI 7600-020; Hitachi, Ibaraki, Japan), and serum concentrations of bilirubin (total and direct), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT) were determined by a Tecfinicon automated biochemical analyzer (TECFINICON RA500/1000; Bayer Corporation, Pittsburgh, PA, USA). The serum concentration of glucose was assayed by the OneTouch Ultra blood glucose meter (Lifescan; Johnson and Johnson Company, Milpitas, CA, USA).

Statistical analysis

The data were analyzed by one-way ANOVA and least significant difference multiple comparison using the software of SPSS (Statistical Package for Social Science, 12.0, SPSS Incorporation, Chicago, IL, USA).

RESULTS

All dogs were healthy and active before xylitol administration. Most dogs became inactive and depressed after xylitol dosing. One low-dose (LD) dog had mild and moderate dystaxia and mild tremors at 1–1.5 h. Two LD and five high-dose (HD) dogs vomited within 0.5–1 h after dosing. All control dogs appeared normal during the study.

Plasma insulin concentrations of both treated groups rose sharply from 20 min after dosing, peaking at 40 min (Table 3). Although there were large variations in insulin concentrations between LD animals, all the LD and HD dogs had increased insulin concentrations. Serum insulin concentrations in the control group were very low (<0.4 μU/mL) throughout the experiment. In contrast to insulin, blood glucose of the LD and HD dogs started to decrease 30 min after the xylitol dose, and were significantly lower than that of the control group at 50 and 60 min ($P < 0.01$) (Table 1). Blood glucose concentrations of both groups then started to rise to concentrations similar to the control value at 1.5 h, and the blood glucose concentration of the LD group was higher than the control value at 2 h. Blood glucose concentrations of both treatment groups returned to baseline values by 3–4 h after dosing.

As shown in Table 2, plasma ALT and AST activities of both treated groups increased dramatically after xylitol administration, and the increase was dose related. The highest serum ALT activities in the LD and HD groups were approximately three- and 10-fold higher than the control value, respectively, and AST activities were increased by around 2.5- and ninefold. Plasma GGT and direct bilirubin were unaffected by xylitol dosing, but total bilirubin was increased in the LD group at 1.5 h and in the HD group at 1–2 h after dosing (Table 3).

Plasma potassium and inorganic phosphorus concentrations were dose-dependently decreased in both treated groups from 20 to 60 min after dosing, respectively (Table 3). The values remained lower than control and predose values at 3 h. Plasma calcium concentrations of LD and HD animals were higher than the concentrations of the control group at 1–3 h, but were not

Table 1. Blood glucose (mmol/L) in dogs before and after feeding xylitol solution

Dose (g/kg)	Time after dosing (min)											
	0	10	20	30	40	50	60	90	120	180	240
0	3.97 ± 0.31	4.24 ± 0.53	4.33 ± 0.57	4.15 ± 0.39	4.13 ± 0.37	4.20 ± 0.24	4.63 ± 0.88	4.35 ± 0.56	4.35 ± 0.67	4.70 ± 0.93	4.40 ± 0.66
1	4.37 ± 1.01	4.90 ± 0.82	4.47 ± 1.36	3.88 ± 1.43	2.93 ± 1.25	2.03 ± 0.82 a**	2.13 ± 0.29 a**	5.42 ± 1.24	7.12 ± 3.31	5.17 ± 1.72	4.10 ± 0.70
4	4.40 ± 0.42	4.57 ± 0.52	4.33 ± 1.13	3.02 ± 1.46	2.75 ± 0.96 b**	2.35 ± 0.53 b**	2.47 ± 0.59 b**	3.50 ± 1.85	4.18 ± 1.39	3.30 ± 1.11 b*c*	4.03 ± 0.81

a – mean that the differences of low-dosing group compared with control group were significant, b – mean that the differences of high-dosing group compared with control group were significant, c – mean the differences of high-dosing group compared with the low dosing group were significant. *$P < 0.05$, **$P < 0.01$.

Table 2. The changes of some enzymes in dogs before and after feeding xylitol solution

Time (h)	ALT (U/L)			AST (U/L)			GGT (U/L)		
	0 g/kg	1 g/kg	4 g/kg	0 g/kg	1 g/kg	4 g/kg	0 g/kg	1 g/kg	4 g/kg
0	34.00 ± 15.95	27.67 ± 9.52	33.83 ± 10.19	34.50 ± 17.42	101.67 ± 36.41 a^{**}	351.33 ± 198.67 $b^{**}c^{*}$	5.67 ± 2.58	6.50 ± 2.59	4.33 ± 2.42
4	34.50 ± 17.42	101.67 ± 36.41 a^{**}	351.33 ± 198.67 $b^{**}c^{*}$	26.17 ± 5.49	70.00 ± 38.51 a^{*}	239.83 ± 125.75 $b^{**}c^{*}$	4.67 ± 0.52	5.67 ± 2.58	6.00 ± 2.61
8	34.67 ± 18.17	102.67 ± 35.85 a^{**}	362.83 ± 178.42 $b^{**}c^{**}$	30.17 ± 14.25	52.67 ± 27.92	145.83 ± 43.21 $b^{**}c^{**}$	5.33 ± 1.21	6.17 ± 1.94	5.83 ± 3.06
12	34.50 ± 20.76	93.00 ± 30.95 a^{**}	341.67 ± 168.47 $b^{**}c^{**}$	26.83 ± 6.11	40.17 ± 15.63	98.17 ± 32.71 $b^{**}c^{**}$	4.67 ± 0.52	5.83 ± 2.14	6.17 ± 3.43
24	34.50 ± 19.59	59.83 ± 27.14	260.50 ± 130.27 $b^{**}c^{**}$	23.00 ± 6.26	23.00 ± 4.65	31.50 ± 12.34	5.33 ± 1.51	5.33 ± 3.27	6.50 ± 2.88
48	35.67 ± 21.13	59.00 ± 13.46 a^{*}	186.67 ± 78.25 $b^{**}c^{**}$	35.17 ± 6.21	21.17 ± 1.60 a^{**}	21.33 ± 4.72 b^{**}	5.83 ± 0.75	6.83 ± 2.23	6.50 ± 2.88
72	31.00 ± 21.46	46.00 ± 10.26	134.67 ± 62.42 $b^{**}c^{**}$	28.00 ± 3.74	20.67 ± 2.50 a^{**}	21.33 ± 5.32 b^{*}	4.83 ± 2.04	6.17 ± 1.94	5.67 ± 6.22
120	42.00 ± 20.85	40.17 ± 9.77	81.17 ± 38.27 c^{*}	29.83 ± 7.03	22.33 ± 8.91	21.17 ± 4.07 b^{*}	6.17 ± 0.75	6.67 ± 3.08	5.83 ± 2.14
168	42.33 ± 18.03	34.83 ± 8.89	57.33 ± 21.38	24.00 ± 4.10	24.67 ± 9.16	23.67 ± 7.71	5.50 ± 1.50	6.83 ± 2.14	6.33 ± 1.75

a – mean that the differences of low-dosing group compared with control group were significant, b – mean that the differences of high-dosing group compared with control group were significant, c – mean the differences of high-dosing group compared with the low dosing group were significant. $^{*}P < 0.05$, $^{**}P < 0.01$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase..

different from the predose values. Plasma chloride and sodium concentrations were unchanged.

DISCUSSION

The purpose of this study was to provide data for the diagnosis and treatment of xylitol poisoning. Our study showed that xylitol toxicity is characterized by hyperinsulinemia, hypoglycemia, hypokalemia, hypophosphatemia, hyperbilirubinemia, and increased serum AST and ALT concentrations. If dogs are suspected of xylitol poisoning from swallowing chewing gums or other xylitol-containing products, clinical pathology should assist differential diagnosis. Supportive therapies such as fluid and electrolyte supplement are recommended.

Xylitol is toxic to dogs if significant amounts are consumed. In our study, dogs receiving an oral dose of 1 or 4 g/kg xylitol exhibited decreased activity, hyperinsulinemia, hypokalemia, hypophosphatemia and increased plasma aminotransferases (ALT and AST). The oral dose of up to 4 g/kg did not cause mortality.

Xylitol stimulates synthesis and secretion of insulin, resulting in hyperinsulinemia in dogs (Kuzuya *et al.*, 1969; Tasaka *et al.*, 1971). The exact mechanism of xylitol-induced increase in insulin secretion is unclear, but a study in anaesthetized dogs indicated that xylitol *per se*, rather than its metabolites, directly stimulate insulin secretion by pancreatic islet β cells (Kuzuya & Kanazawa, 1969). Insulin stimulates the activity of membrane Na^{+}-K^{+}-adenosine-triphosphate (ATPase), which catalyses the intracellular transfer of potassium ion (Allon *et al.*, 1993; Al-Khalili *et al.*, 2003), thus inducing hypokalemia. As expected, increased insulin concentrations resulted in a decrease in blood glucose, and the maximum decrease in blood glucose concentrations occurred 10–20 min after the peak of insulinemia. Clinical signs of weakness and depressed activities were probably a result of hypoglycemia (Dunayer, 2004).

Plasma ALT and AST were dose-dependently increased in dogs dosed with 1 or 4 g/kg xylitol, suggesting hepatic damage. Xylitol is mainly metabolized in the liver (Forster, 1975; Quadflieg & Brand, 1976). It enters into the pentose phosphate pathway, producing the intermediate metabolite, ribose -5-phosphate, before being transformed to glucose (Woods & Krebs, 1973). This metabolic process requires ATP (Vincent *et al.*, 1989). When a large amount of xylitol is absorbed into the blood circulation, ATP in hepatocytes is exhausted, leading to hepatocyte necrosis and thus elevated plasma ALT and AST (Dunayer & Gwaltney-Brant, 2006). The hepatic damage was not associated with effects on the biliary system, as plasma GGT and direct bilirubin concentrations were unchanged in dogs in our study. Increased plasma total bilirubin was detected in our study represented increased indirect bilirubin, which was probably due to hemolysis. It is well known that the continuous supply of blood glucose is critical for not only normal functions of liver and brain but also the integrity of leucocyte and erythrocyte membranes (Feig *et al.*, 1972). Once the supply of glucose is markedly reduced, erythrocyte membranes are ruptured,

Table 3. The serum biochemistry in dogs before and after feeding xylitol solution

Parameters	Dose (g/kg)	Time after dosing (min)					
		0	20	40	60	90	180
Insulin (μU/mL)	0	0.53 ± 0.63	0.51 ± 0.61	0.20 ± 0.00	0.20 ± 0.00	0.20 ± 0.00	0.20 ± 0.00
	1	0.71 ± 0.61	8.11 ± 6.58	8.43 ± 7.14	5.09 ± 4.10	7.08 ± 10.48	2.14 ± 2.33
	4	0.82 ± 0.42	19.39 ± 8.56 b**c*	21.22 ± 4.38 b**c**	16.80 ± 13.33	12.22 ± 12.71	8.15 ± 8.97
D.BILL (μmol/L)	0	0.68 ± 0.38	0.47 ± 0.09	0.67 ± 0.45	0.61 ± 0.37	0.64 ± 0.43	0.55 ± 0.16
	1	0.62 ± 0.34	0.41 ± 0.37	0.49 ± 03.35	0.44 ± 0.27	0.77 ± 0.37	0.58 ± 0.26
	4	0.46 ± 0.27	0.58 ± 0.42	0.52 ± 0.34	0.79 ± 0.32	0.71 ± 0.46	1.54 ± 1.26
T.BILL (μmol/L)	0	2.23 ± 0.39	2.16 ± 0.68	2.54 ± 0.42	2.34 ± 0.39	2.12 ± 0.42	2.22 ± 0.37
	1	2.25 ± 0.53	1.97 ± 0.65	2.68 ± 0.89	2.78 ± 1.00	3.48 ± 0.92 a*	1.71 ± 1.15
	4	2.55 ± 0.77	2.72 ± 0.84	3.35 ± 0.84	3.97 ± 0.95 b**	3.63 ± 0.84 b**	4.61 ± 3.23
K^+ (mmol/L)	0	4.63 ± 0.55	4.64 ± 0.53	4.49 ± 0.58	4.50 ± 0.53	4.49 ± 0.46	4.68 ± 0.35
	1	4.90 ± 0.32	4.75 ± 0.43	4.37 ± 0.42	3.89 ± 0.61	3.52 ± 0.43 a**	4.16 ± 0.33 a*
	4	4.93 ± 0.57	4.90 ± 0.42	4.13 ± 0.33	3.07 ± 0.64 b**c*	3.49 ± 0.44 b**	3.60 ± 0.33 b**c*
Na^+ (mmol/L)	0	148.00 ± 5.06	146.83 ± 2.32	146.50 ± 3.94	146.67 ± 3.01	147.83 ± 2.56	146.67 ± 3.73
	1	149.75 ± 5.02	147.25 ± 3.75	148.28 ± 2.91	148.23 ± 3.40	147.03 ± 2.66	146.77 ± 2.19
	4	148.53 ± 4.19	146.43 ± 3.89	147.13 ± 3.42	148.88 ± 4.84	148.70 ± 3.95	146.43 ± 2.62
Cl^- (mmol/L)	0	112.50 ± 4.14	113.17 ± 3.19	112.33 ± 3.62	113.67 ± 2.66	114.83 ± 3.13	113.00 ± 3.03
	1	114.50 ± 4.09	113.50 ± 4.51	115.00 ± 3.74	114.00 ± 3.58	112.50 ± 3.15	112.33 ± 2.58
	4	112.50 ± 4.23	112.50 ± 3.21	113.83 ± 4.22	107.00 ± 19.56	114.00 ± 3.80	111.67 ± 2.50
Pi (mmol/L)	0	1.47 ± 0.23	1.47 ± 0.27	1.43 ± 0.29	1.43 ± 0.29	1.46 ± 0.27	1.55 ± 0.31
	1	1.57 ± 0.27	1.47 ± 0.32	1.12 ± 0.37	0.78 ± 0.21 a**	0.91 ± 0.46 a*	1.77 ± 0.27
	4	1.44 ± 0.29	1.08 ± 0.19 b*c*	0.78 ± 0.22 b**	0.49 ± 0.28 b**	0.67 ± 0.39 b**	1.10 ± 0.59 c*
Ca^{2+} (mmol/L)	0	2.51 ± 0.07	2.48 ± 0.09	2.47 ± 0.11	2.45 ± 0.08	2.46 ± 0.01	2.50 ± 0.09
	1	2.57 ± 0.06	2.55 ± 0.07	2.52 ± 0.09	2.58 ± 0.08 a*	2.47 ± 0.10	2.46 ± 0.08
	4	2.66 ± 0.14	2.63 ± 0.19	2.59 ± 0.16	2.61 ± 0.12 b*	2.62 ± 0.11 c*	2.63 ± 0.14 c*

The low range value of testing insulin is 0.2. a – mean that the differences of low-dosing group compared with control group were significant, b – mean that the differences of high-dosing group compared with control group were significant, c – mean the differences of high-dosing group compared with the low-dosing group were significant. *$P < 0.05$, **$P < 0.01$. T.BILL, total bilirubin; D.BILL, direct bilirubin; K^+, potassium ion; Na^+, sodium ion; Ca^{2+}, calcium ion; Cl^-, chloride; Pi, inorganic phosphorus.

releasing hemoglobin, which is degraded to bilirubin (Nagy *et al.*, 1998).

It is reported that xylitol can affect the epithelial tissue and promote Ca^{2+} absorption from the small and large intestines *in vitro* (Shimamoto *et al.*, 1995; Mineo *et al.*, 2002). In our study, the concentrations of Ca^{2+} in xylitol-dosed groups were higher than that of the control group, which was in accordance with the results of above-mentioned studies, although the plasma concentrations were similar to predose values of the xylitol-treated animals.

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