NOTE *Internal Medicine*

Single oral dose safety of D-allulose in dogs

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ABSTRACT. Healthy dogs were administered acute oral doses of D-allulose (also called D-psicose) to evaluate its toxicity. Six dogs received oral doses of either a placebo or D-allulose solution (1 and 4 g/kg) on three different study days. One dog experienced vomiting, and five dogs showed transient diarrhea when 4 g/kg of D-allulose was administered. All dogs were active and had a good appetite throughout the study period. Blood glucose concentration slightly decreased without a rise in plasma insulin concentration 2 hr after D-allulose administration. Plasma alkaline phosphatase activities showed a mild increase between 12 and 48 hr after D-allulose administration. These data suggested that a single oral dose of D-allulose does not show severe toxicity in dogs.
KEY WORDS: D-allulose, dog, oral dose, rare sugar, safety

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The International Society of Rare Sugars defines rare sugars as monosaccharides and their derivatives that rarely exist in nature. D-allulose (also called D-psicose) used in this study is one of the rare sugars and is a C-3 epimer of D-fructose. Recently, a novel enzymatic method has enabled a large-scale production of D-allulose [12], and consequently, D-allulose is used as an alternative sweetener. Orally administered D-allulose is absorbed from the intestine and is excreted in the urine [23]. D-allulose provides a very low level of energy [10] and has various favorable biological effects, including lowering of blood glucose [6, 9, 19], protection of pancreatic β-cells [7] and inhibition of body fat accumulation [11, 21]. Although these effects of D-allulose have not yet been fully elucidated, possible mechanisms, such as inhibition of glucose absorption from the intestine [5] and suppression of hepatic lipogenic enzymes [17], have been suggested. From these results, D-allulose is expected to be beneficial for the treatment and prevention of diabetes mellitus and obesity [8].

The prevalence of diabetes mellitus and obesity, a serious problem in companion dogs, is increasing [3, 20]. Considering the beneficial effect of D-allulose, it is also potentially useful for the treatment and prevention of diabetes mellitus and obesity in dogs.

Xylitol is one of the rare sugars and is well-known to cause toxicity, specifically in dogs [2, 14, 24]. Ingestion of xylitol causes hypoglycemia with hyperinsulinemia and hepatic damage and can be life-threatening [2, 14, 24]. Although D-allulose is highly safe in rodents [18, 25] and humans [4] and it is classified as an ordinary substance (dose causing 50% mortality: LD_{50}=16 g/kg) [25], the safety of D-allulose should be confirmed before practical use in dogs because species difference in responses to sugars can be unpredictable [15]. However, no studies have been conducted on the safety of D-allulose in dogs. In the current study, acute oral doses of D-allulose were administered to healthy dogs to evaluate its toxicity.

This study was approved by the Institutional Animal Experiment Committee of Gifu University. Six healthy beagle dogs (one castrated male and five spayed females, 2.5 ± 0.7 years of age and 13.9 ± 1.6 kg of body weight) were used. All dogs were confirmed as healthy by physical examination, complete blood count and plasma biochemical analysis.

D-allulose was provided by the Rare Sugar Research Center in Kagawa University, Japan. Food was withheld from the dogs overnight, after which they received an oral dose of either a placebo or D-allulose solution (1 and 4 g/kg) according to a Latin square design on three different study days at 9:00 AM. The dose rate of D-allulose was determined by reference to the xylitol study [24]. D-allulose dissolved in 100 m*l* of water or 100 m*l* of water as placebo was administered orally with a plastic syringe. Blood samples were taken from the cephalic vein before and 20 min, 40 min, 1, 2, 4, 8, 12, 24, 48, 96 and 144 hr after the oral administrations. Each dog was studied three times with an interval of at least 7 days between each study. Blood samples were placed in heparinized tubes, and plasma was separated by centrifugation (3,000 × g for 15 min at 4°C) and stored frozen at −30°C until analysis. The dogs were allowed free access to water throughout the study. Twelve hours after placebo or D-allulose administration, the dogs were fed commercial maintenance dry food (Royal Canin Medium Adult; Royal Canin Japon, Tokyo, Japan) and thereafter were fed twice daily.

Plasma concentrations of glucose, total calcium, inorganic phosphorus, sodium, potassium, chlorine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alka-

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Table 1. Plasma glucose, insulin and electrolytes in dogs before and after oral D-allulose administration

Parameters	Dose (g/kg)	0 min	20 min	40 min	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr	96 hr	144 hr
Glucose (mg/d*l*)													
	0	102.0 ± 5.1	103.7 ± 6.7	105.2 ± 9.0	104.8 ± 4.1	106.2 ± 3.3	104.7 ± 5.4	103.0 ± 3.8	98.5 ± 1.5	105.8 ± 4.9	103.7 ± 4.5	105.3 ± 5.4	107.0 ± 6.3
	1	99.0 ± 11.2	100.3 ± 4.0	99.2 ± 5.0	101.2 ± 5.5	94.2 ± 2.6[a)]	98.2 ± 4.6	101.0 ± 3.9	94.5 ± 3.3	111.8 ± 12.0[b)]	100.8 ± 2.9	106.2 ± 4.9	101.5 ± 10.3
	4	102.2 ± 5.8	105.6 ± 6.5	103.0 ± 6.3	102.6 ± 3.0	94.6 ± 8.3[a)]	96.8 ± 6.4	98.8 ± 2.9	97.0 ± 5.1	107.2 ± 5.1	100.8 ± 5.8	106.4 ± 5.9	98.0 ± 1.9
Insulin (*n*g/m*l*)													
	0	0.47 ± 0.23	0.38 ± 0.13	0.38 ± 0.25	0.30 ± 0.04	0.45 ± 0.16	ND	ND	ND	ND	ND	ND	ND
	1	0.30 ± 0.07	0.38 ± 0.20	0.29 ± 0.11	0.60 ± 0.68	0.32 ± 0.17	ND	ND	ND	ND	ND	ND	ND
	4	0.36 ± 0.09	0.64 ± 0.56	0.41 ± 0.19	0.59 ± 0.39	0.30 ± 0.10	ND	ND	ND	ND	ND	ND	ND
Total calcium (mg/d*l*)													
	0	10.9 ± 1.1	10.1 ± 0.3[b)]	10.1 ± 0.2[b)]	10.0 ± 0.3[b)]	10.0 ± 0.3[b)]	10.4 ± 0.4	10.4 ± 0.5	10.4 ± 0.3	10.2 ± 0.2	10.6 ± 0.4	10.4 ± 0.4	10.1 ± 0.6
	1	10.6 ± 0.4	10.6 ± 0.6	10.4 ± 0.6	10.3 ± 0.5	10.4 ± 0.6	10.8 ± 0.3	10.7 ± 0.5	10.6 ± 0.3	8.6 ± 4.2	10.8 ± 0.4	10.4 ± 0.6	10.5 ± 0.3
	4	11.1 ± 0.9	10.9 ± 0.4	10.9 ± 0.4	10.7 ± 0.2	10.0 ± 0.6[b)]	10.6 ± 0.4	10.7 ± 0.7	10.6 ± 0.6	10.2 ± 0.3	10.6 ± 0.4	10.4 ± 0.6	10.4 ± 0.1
Inorganic phosphorus (mg/d*l*)													
	0	4.33 ± 0.78	3.87 ± 0.71	3.93 ± 0.74	3.83 ± 0.72	3.90 ± 0.76	4.68 ± 1.07	4.47 ± 0.78	4.73 ± 1.05	5.42 ± 0.89	4.42 ± 0.65	4.80 ± 0.58	4.23 ± 0.56
	1	4.03 ± 0.92	3.62 ± 0.79	3.12 ± 0.78	3.00 ± 0.72	3.35 ± 0.86	5.23 ± 1.52	5.47 ± 0.85[b)]	5.08 ± 0.32	5.65 ± 0.86[b)]	4.73 ± 0.58	4.78 ± 0.55	4.92 ± 0.70
	4	4.32 ± 0.53	3.80 ± 0.42	3.68 ± 0.36	3.58 ± 0.43	3.18 ± 0.54[b)]	5.52 ± 0.62[b)]	5.92 ± 0.92[a,b)]	5.72 ± 1.06[b)]	4.52 ± 0.64	4.40 ± 0.44	4.52 ± 0.34	4.42 ± 0.79
Sodium (mEq/*l*)													
	0	149.0 ± 1.3	147.2 ± 1.7	147.5 ± 1.4	147.2 ± 1.0	150.3 ± 5.7	148.2 ± 1.5	148.5 ± 1.0	147.8 ± 1.2	148.8 ± 1.5	147.0 ± 1.4	149.7 ± 3.1	150.2 ± 5.5
	1	148.0 ± 1.5	148.0 ± 1.3	147.0 ± 2.5	145.8 ± 2.6	147.8 ± 3.4	147.3 ± 0.8	147.8 ± 1.2	147.2 ± 0.8	149.3 ± 1.9	147.3 ± 0.8	148.0 ± 0.9	147.8 ± 0.8
	4	149.2 ± 1.5	150.6 ± 1.8	150.8 ± 1.9	151.0 ± 3.2	143.4 ± 3.78[b)]	146.6 ± 2.2	147.2 ± 0.8	146.0 ± 0.7	148.8 ± 1.3	147.2 ± 0.4	148.0 ± 0.7	148.6 ± 1.3
Potassium (mEq/*l*)													
	0	4.40 ± 0.09	4.10 ± 0.17	4.00 ± 0.15[b)]	4.03 ± 0.31[b)]	4.00 ± 0.38[b)]	4.03 ± 0.10[b)]	4.15 ± 0.14	4.10 ± 0.17	4.37 ± 0.22	4.30 ± 0.23	4.25 ± 0.24	4.35 ± 0.23
	1	4.32 ± 0.15	4.10 ± 0.15	3.97 ± 0.15[b)]	3.98 ± 0.22	3.92 ± 0.25[b)]	4.02 ± 0.22	4.22 ± 0.26	4.08 ± 0.15	4.47 ± 0.26	4.25 ± 0.19	4.27 ± 0.25	4.10 ± 0.22
	4	4.22 ± 0.16	4.06 ± 0.47	4.06 ± 0.42	4.10 ± 0.44	3.78 ± 0.47	3.76 ± 0.40	4.02 ± 0.26	3.92 ± 0.31	4.38 ± 0.13	4.16 ± 0.13	4.24 ± 0.15	4.08 ± 0.11
Chlorine (mEq/*l*)													
	0	116.7 ± 1.9	114.8 ± 2.0	114.0 ± 2.5	115.5 ± 2.1	118.0 ± 3.3	117.5 ± 3.1	117.7 ± 2.4	117.7 ± 2.1	115.0 ± 1.5	111.5 ± 2.7[b)]	117.3 ± 2.7	116.8 ± 3.1
	1	115.8 ± 3.2	116.5 ± 1.4	114.8 ± 2.3	115.5 ± 2.6	116.8 ± 3.6	115.3 ± 1.8	115.3 ± 1.4	115.2 ± 1.8	116.3 ± 2.5	112.7 ± 2.7	114.5 ± 3.1	112.3 ± 3.1
	4	116.8 ± 2.2	119.8 ± 4.0	118.8 ± 3.5	119.0 ± 3.0	112.2 ± 2.5	114.6 ± 4.6	114.4 ± 1.5	114.4 ± 3.2	114.8 ± 2.6	113.0 ± 1.7	114.8 ± 1.6	113.6 ± 2.5

Data were presented as mean ± SD of six dogs, except for the 4 g/kg group (n=5). a) $P<0.05$ vs. the value in control group. b) $P<0.05$ vs. the value before administration. ND: Not determined.

Table 2. Plasma biochemistry in dogs before and after oral D-allulose administration

Parameters	Dose (g/kg)	0 hr	4 hr	8 hr	12 hr	24 hr	48 hr	96 hr	144 hr
Alanine aminotransferase (U/*l*)									
	0	48.2 ± 22.4	47.5 ± 19.8	48.3 ± 19.5	47.2 ± 18.0	43.5 ± 18.4	41.3 ± 14.1	39.5 ± 9.3	37.0 ± 6.2
	1	48.8 ± 10.5	48.8 ± 9.2	51.0 ± 8.5	50.8 ± 9.0	49.2 ± 7.9	49.3 ± 8.9	46.5 ± 9.7	42.7 ± 10.6
	4	47.2 ± 17.7	50.8 ± 18.8	51.2 ± 17.5	51.4 ± 18.2	47.6 ± 15.9	51.0 ± 18.6	48.0 ± 15.4	40.6 ± 8.3
Aspartate aminotransferase (U/*l*)									
	0	24.3 ± 1.9	28.5 ± 3.1	27.7 ± 4.4	27.3 ± 4.1	22.3 ± 1.6	28.3 ± 4.3	25.8 ± 3.1	25.2 ± 3.1
	1	29.8 ± 4.6	37.3 ± 15.6	37.7 ± 20.8	37.3 ± 21.5	31.2 ± 18.6	31.3 ± 8.9	27.7 ± 3.1	26.5 ± 3.9
	4	30.2 ± 5.7	41.8 ± 18.5	43.8 ± 24.0	45.4 ± 23.9	42.8 ± 20.3	57.4 ± 53.0	28.2 ± 7.0	26.2 ± 4.1
Alkaline phosphatase (U/*l*)									
	0	143.2 ± 24.1	141.2 ± 19.6	147.8 ± 27.2	146.8 ± 29.5	143.2 ± 26.6	144.5 ± 24.3	136.5 ± 29.4	129.5 ± 29.9
	1	148.0 ± 29.0	161.3 ± 24.5	182.0 ± 26.9	193.8 ± 40.7	199.3 ± 47.4 [a)]	196.5 ± 39.5 [a)]	169.0 ± 37.9	157.2 ± 43.8
	4	168.0 ± 60.4	189.0 ± 52.3	218.8 ± 44.0 [b)]	237.6 ± 42.1 [a,b)]	257.6 ± 18.7 [a,b)]	216.6 ± 29.8 [a)]	171.6 ± 27.8	155.0 ± 26.1
Total bilirubin (mg/d*l*)									
	0	0.12 ± 0.04	0.13 ± 0.05	0.10 ± 0.00	0.10 ± 0.00	0.10 ± 0.00	0.18 ± 0.10	0.15 ± 0.08	0.18 ± 0.08
	1	0.15 ± 0.08	0.13 ± 0.05	0.10 ± 0.00	0.18 ± 0.16	0.13 ± 0.05	0.17 ± 0.08	0.15 ± 0.08	0.20 ± 0.06
	4	0.14 ± 0.05	0.12 ± 0.04	0.10 ± 0.00	0.12 ± 0.04	0.12 ± 0.04	0.18 ± 0.08	0.18 ± 0.13	0.16 ± 0.05
Urea nitrogen (mg/d*l*)									
	0	7.50 ± 6.65	6.22 ± 5.32	5.58 ± 4.91	5.35 ± 4.61	8.90 ± 6.90	5.95 ± 4.78	9.08 ± 6.86	6.65 ± 5.28
	1	10.62 ± 3.97	8.53 ± 1.43	8.07 ± 1.35	7.65 ± 1.71	14.12 ± 2.42	9.33 ± 1.72	11.00 ± 3.50	12.20 ± 2.90
	4	9.88 ± 1.46	8.58 ± 1.80	7.72 ± 1.55	7.12 ± 1.54	12.86 ± 1.53	9.80 ± 1.83	12.20 ± 4.46	11.30 ± 2.90
Creatinine (mg/d*l*)									
	0	0.45 ± 0.08	0.45 ± 0.08	0.42 ± 0.08	0.45 ± 0.08	0.48 ± 0.08	0.42 ± 0.08	0.42 ± 0.08	0.43 ± 0.08
	1	0.45 ± 0.05	0.38 ± 0.08	0.40 ± 0.06	0.43 ± 0.05	0.45 ± 0.10	0.38 ± 0.08	0.42 ± 0.08	0.40 ± 0.06
	4	0.40 ± 0.00	0.36 ± 0.05	0.38 ± 0.04	0.36 ± 0.05	0.40 ± 0.00	0.42 ± 0.04	0.38 ± 0.04	0.38 ± 0.04
Total protein (g/d*l*)									
	0	6.15 ± 0.26	6.13 ± 0.44	6.23 ± 0.23	6.17 ± 0.29	6.07 ± 0.24	6.35 ± 0.26	6.25 ± 0.37	6.28 ± 0.41
	1	6.27 ± 0.40	6.17 ± 0.44	6.23 ± 0.31	6.32 ± 0.23	6.17 ± 0.37	6.35 ± 0.43	6.35 ± 0.33	6.38 ± 0.36
	4	6.44 ± 0.30	6.36 ± 0.22	6.46 ± 0.25	6.44 ± 0.15	6.16 ± 0.30	6.34 ± 0.29	6.44 ± 0.21	6.38 ± 0.18
Albumin (g/d*l*)									
	0	3.42 ± 0.39	3.35 ± 0.15	3.42 ± 0.21	3.38 ± 0.13	3.10 ± 0.09	3.43 ± 0.18	3.33 ± 0.19	3.43 ± 0.12
	1	3.52 ± 0.13	3.40 ± 0.18	3.47 ± 0.18	3.53 ± 0.14	3.33 ± 0.23	3.42 ± 0.17	3.38 ± 0.25	3.43 ± 0.23
	4	4.14 ± 1.45	4.08 ± 1.31	4.16 ± 1.38	4.10 ± 1.42	3.82 ± 1.45	3.96 ± 1.38	3.94 ± 1.39	4.00 ± 1.30
Total cholesterol (mg/d*l*)									
	0	161.2 ± 33.9	152.2 ± 34.3	156.2 ± 35.7	150.3 ± 33.3	154.3 ± 29.4	171.3 ± 33.5	175.0 ± 39.3	180.3 ± 44.5
	1	181.8 ± 40.8	174.3 ± 42.1	170.2 ± 39.1	176.7 ± 34.7	172.7 ± 28.4	179.5 ± 48.0	182.3 ± 40.5	193.5 ± 45.3
	4	191.4 ± 43.9	182.2 ± 42.5	184.6 ± 53.8	182.4 ± 51.1	165.8 ± 12.0	193.6 ± 51.8	185.4 ± 36.5	201.4 ± 34.1
Triglyceride (mg/dl)									
	0	41.7 ± 18.3	35.8 ± 13.5	32.0 ± 9.6	26.7 ± 5.8	43.3 ± 5.1	49.3 ± 8.8	48.3 ± 23.0	60.0 ± 19.2
	1	46.0 ± 10.5	45.2 ± 14.6	36.8 ± 11.5	30.5 ± 6.9	60.0 ± 26.3	53.7 ± 11.4	63.2 ± 22.5	63.0 ± 19.9
	4	43.0 ± 10.5	38.8 ± 12.7	37.2 ± 12.5	33.2 ± 7.7	39.8 ± 9.1	44.8 ± 7.0	61.2 ± 11.2	43.6 ± 11.3

Data were presented as mean ± SD of six dogs, except for the 4 g/kg group (n=5). a) $P<0.05$ vs. the value in control group. b) $P<0.05$ vs. the value before administration.

line phosphatase (ALP), total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol and triglyceride were determined using an automated biochemical analyzer (DRI-CHEM 7000; Fujifilm, Tokyo, Japan). Plasma insulin concentrations until 2 hr after the D-allulose administration were assayed using the LBIS dog insulin enzyme-linked immunosorbent assay kit (Sibayagi, Shibukawa, Japan) [22].

Data are shown as mean ± SD. Differences among D-allulose dose rate and differences between values before and during the test were analyzed by one-way ANOVA with the Tukey–Kramer test and the Dunnett test. Values of $P<0.05$ were considered significant. These statistics analyses were carried out in Excel 2011 (Microsoft, Redmond, WA, U.S.A.) with the add-in software Statcel 3 (OMS Publishing, Tokorozawa, Japan).

One dog experienced vomiting shortly after oral administration of 4 g/kg of D-allulose, and thus, the dog was excluded from further analysis. The remaining five dogs who received 4 g/kg of D-allulose did not show vomiting; however, the dogs experienced transient diarrhea between 2 and 24 hr after administration. Two dogs showed transient nausea within 1 hr after receiving a 1 g/kg dose of D-allulose. No other symptoms were observed and all dogs were active, and had a good appetite throughout the study.

Results of biochemical and hormonal analyses are shown in Tables 1 and 2. The blood glucose concentration showed a slight decrease ($P<0.05$) 2 hr after the administration of 1 g/kg or 4 g/kg of D-allulose. Plasma ALP activities showed a mild, dose-dependent increase ($P<0.05$) between 12 and 48 hr after D-allulose administration. Plasma inorganic phos-

phorus concentration showed a mild decrease followed by a transient increase within 12 hr. Moreover, plasma inorganic phosphorus concentration in dogs that received 4 g/kg D-allulose was slightly higher ($P<0.05$) than that in control dogs at 8 hr after dose administration. There were no statistical differences in other parameters among the dose rates.

This is the first study on the effects of D-allulose administered in dogs. Our data showed that D-allulose does not show the same degree of toxic potency as xylitol. The dose rate of D-allulose used in the current study was relatively high when compared with that in studies evaluating the physiological effects of D-allulose in humans [4, 9]. Therefore, D-allulose might be safely administered in dogs, although further studies evaluating the long-term safety of D-allulose are required.

Oral doses of D-allulose at 1 or 4 g/kg induced mild and transient gastrointestinal signs. In rodents, an oral dose of D-allulose at 8 g/kg additionally caused transient diarrhea [18]. These symptoms are common in high dose administration of other sugars and are known to be caused by a rise in the enteric osmotic pressure [13]. Therefore, the gastrointestinal signs observed in the current study after oral D-allulose administration were considered as non-specific responses.

D-allulose administration decreased plasma glucose concentration without an increase in plasma insulin concentrations. In addition, the decrease in plasma glucose concentration was relatively small; however, it was not of the level that causes hypoglycemia. This is in contrast with xylitol, which caused severe hypoglycemia by hypersecretion of insulin [24]. D-allulose additionally suppressed blood glucose concentration in humans [4, 9]. Possible mechanisms for the glucose suppressive effect of D-allulose could be enhancement of glucokinase activity to stimulate the synthesis of glycogen in the liver [6], and inhibition of glucose absorption from the intestine [5]. Although the mechanism of hypoglycemic effect of D-allulose is not completely understood, the authors consider that D-allulose would not cause severe hypoglycemia in healthy dogs.

Plasma ALP activity increased in a dose-dependent manner after D-allulose administration. A limitation of this study is the lack of histological data. Histological examination of the liver might have revealed the mechanism for the increment in plasma ALP activity. However, the increment in ALP activity was mild and transient without a significant rise in other hepatic enzymes. In contrast, administration of 1 or 4 g/kg of xylitol induced marked increases in hepatic enzymes (ALT, AST and ALP) with hyperbilirubinemia being manifested 4 to 120 hr after administration [24]. Although a large dose of D-allulose may cause stress to the liver and lead to a transient increase in plasma ALP activity, we conclude that D-allulose does not show the same degree of severe hepatotoxicity as xylitol.

Plasma inorganic phosphorus concentration is altered under various conditions, including abnormalities in intestinal absorption, renal excretion and transcellular shifts, or hemolysis [1]. Furthermore, plasma inorganic phosphorus concentration shows significant diurnal variation, showing peaks at 5:00 AM and 5:00 PM in dogs [16]. The result of plasma inorganic phosphorus concentration in this study was consistent with the diurnal variation reported. However, dogs that received D-allulose showed a larger fluctuation in plasma inorganic phosphorus concentration. Although no possible causes of inorganic phosphorus alteration were observed in the current study, the administration of D-allulose may mildly exaggerate the diurnal pattern of plasma inorganic phosphorus concentration in dogs.

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