

Tolerance to Subchronic, High-Dose Ingestion of Erythritol in Human Volunteers

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Erythritol is a sugar alcohol (polyol) which is absorbed from the small intestine in substantial amounts, not metabolized in the human body, and therefore excreted in the urine. Erythritol holds promise as a low-calorie sugar substitute. Human tolerance to repeated oral doses of erythritol was examined in a double-blind, two-way crossover study in 12 healthy, male volunteers. The participants consumed erythritol and, for comparison, sucrose for a duration of 7 days each. The daily dose of the test compounds ingested was 0.3 g/kg on Day 1, 0.6 g/kg on Day 2, and 1.0 g/kg on subsequent days. The daily dose was consumed under supervision in five portions, i.e., with the three main meals, a midmorning snack, and during the afternoon. The test compounds were incorporated into yoghurt, cookies, soft drinks, and chocolate. On each treatment day, body weight and blood pressure were measured and the participants were interviewed about side effects and their perception of stool and urine production. During the last 96 hr of each treatment period, urine was collected at 3-hr intervals during the day and for a 9-hr interval overnight for analysis of erythritol and different urinary parameters. On Days 3 to 7 of each treatment period, the participants were institutionalized. Body weights and blood pressure remained stable during the entire study. Signs of gastrointestinal intolerance were not seen and stool frequency and appearance were not different between the two treatments. The intake of liquids, which were provided *ad libitum*, was generally rather high (32.8 g/kg body wt/day on average) but not different between erythritol and sucrose consumption. Urine output also was high during both treatment periods. About 78% of ingested erythritol was excreted in the urine which led to a higher urinary osmolality but did not influence the 24-hr output of creatinine, citrate, urea, or electrolytes (Na⁺, K⁺, Cl⁻, P_i). The excretion of calcium was slightly higher during the erythritol test period but in

absolute terms this increase was small. The urinary excretions of albumin, β_2 -microglobulin, and *N*-acetylglucosaminidase were slightly elevated during the erythritol test period but they were still well within the physiological range. None of the observed urinary changes became more pronounced with increasing duration of the erythritol treatment. In conclusion, the results of the present study demonstrate that the repeated ingestion of erythritol at daily doses of 1 g/kg body wt was well tolerated by humans. © 1996 Academic

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INTRODUCTION

Erythritol is a sugar alcohol (polyol) which holds promise as a new bulk sweetener, for example for the production of sugarfree and calorie-reduced chocolate, candies, and chewing gum. Like other sugar alcohols, erythritol can also fulfill other technical functions in food, e.g., as a humectant, texturizer, or cryoprotectant (Goossens and Röper, 1994).

In comparison to the sugar alcohols which are presently used for these purposes, such as sorbitol, erythritol has the advantage of a higher gastrointestinal tolerance and a lower physiological energy value (Noda *et al.*, 1994). Because erythritol has a smaller molecular volume than the currently applied polyols, its absorption by passive diffusion from the small intestine proceeds at a faster rate and is henceforth also more complete. It is thought that the better gastrointestinal tolerance, which was observed in humans after the administration of single doses of erythritol, is also a result of this faster and more complete disappearance from the small-intestinal lumen.

Since absorbed erythritol is not metabolized to any significant extent, it has no caloric value. Only the small unabsorbed fraction of erythritol, which is fermented by the colonic microflora to metabolizable short-chain fatty acids, provides energy which is estimated at less than 0.5 kcal/g (Bornet *et al.*, 1992; Noda *et al.*, 1994).

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Absorbed, but not metabolized, erythritol is excreted by the kidneys. Studies in humans have shown that about 80–90% of the ingested erythritol dose is excreted in the urine (Bornet *et al.*, 1992; Hiele *et al.*, 1993; Noda *et al.*, 1994).

The safety of erythritol has been established in standard toxicity tests which include *in vitro* tests for mutagenicity and clastogenicity, subchronic toxicity tests in mice, rats, and dogs, a chronic toxicity/carcinogenicity study in rats, a multigeneration study in rats, and two teratogenicity studies, in rats and in rabbits (Kawamura *et al.*, 1996; Til *et al.*, 1996; Til and Modderman, 1996; Lina *et al.*, 1996; Dean *et al.*, 1996; Waalkens-Berendsen *et al.*, 1996; Smits-van Prooije *et al.*, 1996; Shimizu *et al.*, 1996). Except for certain unspecific effects that are generally observed in rodents in response to the ingestion of polyols (cecal enlargement, pelvic nephrocalcinosis), no signs of an erythritol-mediated toxicity were noted in any of these studies. In particular, adverse effects on the kidneys due to the excretion of large amounts of erythritol were not seen on histopathological examination.

The present study was conducted in order to examine the gastrointestinal tolerance and diuretic response to the repeated ingestion of high oral doses of erythritol in healthy male volunteers. Previous metabolic studies in humans had established that single doses of up to 0.3 g/kg body wt (bw) are well tolerated (Hiele *et al.*, 1993; Noda *et al.*, 1994). For this study, the total daily erythritol dose was set at 1 g/kg bw/day. During the control period, sucrose was administered at the same daily dose. In view of the intended use of erythritol as a sugar substitute, sucrose was considered to be an adequate control.

MATERIALS AND METHODS

Subjects

The study was carried out with 12 healthy, male volunteers between 22 and 46 years of age and having a body weight within the normal range (64.6–98.0 kg). Eight of the volunteers were regular smokers (Table 1). The general medical history of the subjects revealed no evidence of any preexisting organic (especially kidney- or bladder-related) or psychiatric disease, drug allergy, drug or alcohol abuse, or long-term use of pharmaceuticals. The subjects reported no use of any medication during the week before the start of the study and no signs of illness within the previous 2 weeks.

Study Design and Treatments

The study was designed as a double-blind, two-way crossover study. The 14-day protocol comprised two treatment periods with administration of erythritol and sucrose for 7 days each. Six randomly selected subjects received erythritol in the first and sucrose in the

TABLE 1
Personal Data and Sequence of Treatments of 12 Male Volunteers Ingesting Erythritol or Sucrose at up to 1 g/kg bw/Day for Periods of 1 Week Each

Subject No.	Sequence of treatments	Age (years)	Height (cm)	Body weight at start (kg)
1	S-E	35	167	71.1
2 ^a	E-S	22	203	98.0
3 ^a	S-E	46	176	70.0
4 ^a	S-E	46	170	80.0
5 ^a	E-S	34	180	73.7
6	E-S	37	175	77.4
7 ^a	E-S	39	182	70.9
8 ^a	S-E	22	185	94.0
9	E-S	26	183	91.5
10	S-E	31	171	67.5
11 ^a	S-E	34	184	83.1
12 ^a	E-S	33	166	64.6
Mean		33.8	178.5	78.6
±SD		7.9	10.2	11.0

Note. Abbreviations: S, sucrose; E, erythritol.

^a Regular smoker.

second week; for the other six subjects the sequence of the treatments was reversed. The subjects were not informed about their dosing sequence.

Each treatment period started on a Saturday morning and ended on a Friday evening. In order to adapt the subjects to the treatments, the test compounds were provided at a dose of 0.3 g/kg bw on Saturdays and 0.6 g/kg bw on Sundays (adaptation period). Exposure to the full dose of 1 g/kg bw began on Monday morning and ended on Friday evening (test period).

The total daily dose of 1 g/kg bw of erythritol or sucrose was consumed in five portions. At breakfast (8 AM), about 20% of the total daily dose was consumed, at coffee break (10:30 AM) about 10%, at lunch (12:30 AM) about 30%, during afternoons (12:30 AM–7 PM) about 20%, and at dinner (7 PM) about 20%. In practice, fixed amounts of the test compounds were given with test foods at each meal except for dinner at which time the test compounds were dosed individually so as to reach the nominal dose level of 1 g/kg bw/day for each subject. The test substances were given with yogurt (breakfast, dinner), cookies (breakfast, morning coffee), soft drink (lunch), and chocolate (afternoon).

At the start of the adaptation periods, the volunteers received the required amounts of the test foods for unsupervised consumption at home. They were asked to record on a special form all foods and drinks (test and ordinary products) which they consumed during the 2-day adaptation period. During the test periods, the test foods were provided at each mealtime, and the consumption of meals and test foods was supervised. All meals were provided by the canteen of the IPHAR institute and were identical for all volunteers and for each

study period. Beverages, such as mineral water and fruit juice, were allowed *ad libitum* but the consumption of coffee or tea was limited to four cups per day. The volunteers were asked to abstain from excessive alcohol intake during the adaptation period. During the test periods, no alcoholic beverages were consumed.

The two test compounds, erythritol and sucrose, were obtained from Cerestar (Vilvoorde, Belgium). Erythritol was reported to have a dry matter content of $\geq 99.5\%$ and a purity (on a dry matter basis) of $\geq 99.9\%$ (by HPLC). Sucrose was of regular food-grade quality. The test cookies and chocolates with sucrose or erythritol were prepared by Cerestar's Application Center Food (Vilvoorde, Belgium). Yoghurts and soft drinks were sweetened with the two test compounds by canteen-staff of the IPHAR Institute shortly before consumption.

Observations

During the week prior to start of the study, each subject was subjected to a routine medical examination. Compliance with the inclusion and exclusion criteria was assessed, and height and body weight were measured.

During the 2-day adaptation periods, each participant recorded their food and beverage consumption on daily report sheets. During the 5-day test periods, food and beverage intake was recorded by staff of the IPHAR Institute.

On each day of the two test periods, body weight and sitting blood pressure were measured. Each subject was interviewed about their subjective perception of general well-being, satisfaction with the offered test foods, feelings of hunger and thirst, desire for sweet or salty foods, and subjective perception of regularity, consistency, and quantity of stool, frequency and quantity of urine, gastrointestinal intolerance, and other side effects.

Urine was collected during the two test periods in 3-hr intervals during the day (five portions representing urine produced from 7 AM to 10 PM) and one overnight interval (representing urine produced from 10 PM to 7 AM). From the time of collection until the next morning when volume, pH, and osmolality were measured, all urine samples were stored at 4°C. Thereafter, four aliquots (5 ml) of each sample were frozen (without prior centrifugation) to -20°C by putting them in an ordinary deep-freezer. After termination of the second treatment period, two aliquots of each sample were sent to Hôtel-Dieu (F.D.) for analysis of the different urinary parameters, and another aliquot to Cerestar for analysis of erythritol. The fourth aliquot was retained at the IPHAR Institute for potential later, unscheduled analyses. During the transport, the urine samples were kept frozen with dry ice. After receipt at their destination and prior to analysis the aliquots for

analysis of erythritol were stored at -20°C for about 3–4 weeks. The aliquots destined for analyses of all other urinary parameters were kept at -80°C for about 2–4 weeks.

For determination of the urinary electrolytes, enzymes, proteins, urea, and creatinine, the urines were thawed at room temperature, vortexed, and centrifuged (3000 rpm, 20 min, 4°C). The supernatants were then analyzed for sodium (Na^+), potassium (K^+), chloride (Cl^-), calcium (Ca^{2+}), phosphate (P_i), citrate, γ -glutamyl transferase (GGT), *N*-acetyl glucosaminidase (NAG), β_2 -microglobulin ($\beta_2\text{M}$), urea, and creatinine using the methods specified in Table 2. Although GGT was analyzed, the data are not reported. A subsequent study demonstrated that the storage conditions for urine used in this study were not appropriate for GGT (Loeb and Das, 1996).

For determination of erythritol, the urine samples were thawed, vortexed, and filtered through a 0.45- μm filter; 1,3-butanediol was added as an internal standard. HPLC was performed on a Shodex Ionpack column KC 811 (0.8 \times 300 mm) at 75°C using 1.8 mM H_2SO_4 as an eluant (sample volume, 5 μl ; flow rate, 1 ml/min). Erythritol and 1,3-butanediol were detected in the effluent by measurement of the refractive index (Waters RI-Detector R401).

Data Analysis, Statistical Tests

The data on body weight, systolic and diastolic blood pressure, and fluid intake were analyzed by repeated-measures analysis of variance (ANOVA) (Wiener, 1977). For each of these parameters, 120 observations (i.e., 2 treatments \times 5 observation days \times 12 subjects) were available for statistical analysis.

From the data on urinary electrolyte, enzyme, protein, urea, and creatinine concentrations (i.e., mmol/liter, U/liter, $\mu\text{g/liter}$), the respective hourly outputs (i.e., mmol/hr, U/hr, $\mu\text{g/hr}$) as well as excretions relative to that of creatinine (i.e., mmol/mmol creatinine, U/mmol creatinine) were calculated. From the data on hourly outputs and excretions relative to that of creatinine, as well as from the data on pH, osmolality, and conductivity, 24-hr means were then calculated for each subject and each treatment day. For calculating these means it was taken into account that the overnight sample represented a period 3 times longer (9 hr) than the samples collected during the daytime (3 hr each). The urine flow was expressed in ml/hr for each sampling interval, and time-weighted 24-hr means were calculated as well. For calculating the 24-hr means of the different parameters, the urine produced between 10 PM of Day 3 (i.e., urine collected at 7 AM of Day 4) and 10 PM of Day 4 (i.e., urine collected at 10 PM of Day 4) was considered to represent the first full 24-hr cycle. In this way, four complete 24-hr cycles were available for evaluation for each of the two treatment periods

TABLE 2
Assessment of Urinary Parameters

Parameter	Method	Test kit/ equipment
Osmolarity	Freezing point depression	a
Sodium	Ion-specific electrode	b
Potassium	Ion-specific electrode	b
Chloride	Ion-specific electrode	b
Calcium	Colorimetric with <i>o</i> -cresolphthalein complexon	c, d
Phosphate	Colorimetric with phosphomolybdate	c, e
Citrate	Enzymatic with citrate lyase	c, f
γ -Glutamyltransferase	Colorimetric with γ -glutamyl-4-nitroanilide as substrate	c, g
<i>N</i> -Acetyl glucosaminidase	Colorimetric with 3-cresolsulfonphthaleinyl- <i>N</i> -acetyl- β -D-Glucosaminide as substrate	c, h
Creatinine	Colorimetric (Jaffé reaction)	i, j
β_2 -Microglobulin	Nephelometric	k, l
Albumin	Nephelometric	k, m
Urea	Measurement of urease-mediated increase of conductivity	i, n

Note. a, Osmometer, Advanced Instruments (Model 3D); b, Beckman Electrolytes (Nos. 441970, 443300, 441930) with electrolyte reference (No. 443315), buffer (No. 443325), and calibrating solutions (Nos. 443360 and 443365), Beckman Instruments, 93220 Gagny, France; Hitachi 705 autoanalyzer; d, Test kit, Boehringer Mannheim (No. 1125605); e, Test kit, Boehringer Mannheim (No. 836281); f, Test kit, Boehringer Mannheim (No. 139076); g, Test kit, Biotrol (No. A 3029) (400 μ l reagent + 12 μ l urine incubated at 30°C for 7 min, measurement of 4-nitroanilide at 415 nm); h, Test kit and standard, Boehringer Mannheim (Nos. 875406 and 982962), measurement at 30°C; i, Beckman Synchron CX₃ autoanalyzer; j, Test kit and standards, Beckman (Nos. 443340, 443360, 443365); k, BNA (Behring Nephelometer Analyzer); l, Test kit and standards, Biomedical Diagnostics (Nos. N 52241, 52804, 5230); m, Test kit, Behring (SAU, SAL15, SKE, UMT51, UMS51); n, Test kit and standards, Beckman (Nos. 443350, 443360, 443365).

(urine produced between 10 PM of Day 3 and 10 PM of Day 7).

For the statistical assessment of treatment-related differences of urinary parameters, a repeated-measures ANOVA was applied to the 24-hr mean values (2 treatments \times 12 subjects \times 4 24-hr periods = 96 observations for each parameter). Since one of the assumptions of ANOVA is that the residuals from the model are approximately normally distributed, the normality (Shapiro–Wilk test), skewness, and kurtosis of the data were examined. Where the conditions for ANOVA were not fulfilled, inverse scores of ranks were calculated and the repeated-measures ANOVA was applied to these transformed values.

For descriptive analysis, the hourly outputs of urine, NAG, β_2 M, and erythritol and the excretion of osmotically active solutes (mOsm/liter; mOsm/hr) were depicted graphically for each test period (i.e., excretion profiles from 7 AM of Day 3 to 10 PM of Day 7).

Ethical Standards and GCP Compliance

The study was performed in accordance with the declaration of Helsinki. Consent for the study protocol and the participant's consent forms were obtained from the IPHAR IRB (constituted according to FDA guidelines) and the Bayerische Landesärztekammer (Bavarian Chamber of Surgeons). All subjects were properly informed about the purpose and possible risks of the study, and voluntary, written, and witnessed consent was obtained from each participant. The part of the

study performed at the IPHAR Institute was conducted according to GCP guidelines.

RESULTS

All 12 subjects who entered the study completed it according to the protocol. During the two test periods (i.e., Days 3–7 of each treatment period), the mean body weights varied only slightly. A treatment-related difference was not observed (Table 3). All blood pres-

TABLE 3
Body Weight and Blood Pressure of 12 Male Volunteers Ingesting Erythritol or Sucrose at up to 1 g/kg bw/Day for Periods of 1 Week Each

Treatment	Body weight (kg)	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)
Erythritol			
Day 3	79.0 \pm 10.6	136 \pm 10	80 \pm 10
Day 4	79.0 \pm 10.7	129 \pm 7	74 \pm 7
Day 5	79.0 \pm 10.7	123 \pm 9	68 \pm 9
Day 6	78.8 \pm 10.9	121 \pm 8	62 \pm 11
Day 7	79.1 \pm 10.8	123 \pm 14	71 \pm 16
Sucrose			
Day 3	79.2 \pm 11.0	138 \pm 8	75 \pm 10
Day 4	79.0 \pm 11.1	129 \pm 14	72 \pm 9
Day 5	78.8 \pm 10.7	122 \pm 8	67 \pm 10
Day 6	79.1 \pm 11.1	122 \pm 11	68 \pm 10
Day 7	79.3 \pm 11.0	126 \pm 12	73 \pm 11

Note. Values are means \pm SD of 12 subjects. B.P., blood pressure. Statistical test: repeated-measures ANOVA.

TABLE 4
Bodyweight, Liquid Intake, and Urine Production of 12 Male Volunteers Ingesting Erythritol or Sucrose at up to 1 g/kg bw/Day for Periods of 1 Week Each

Subject no.	Body weight (kg)		Liquid intake (ml/day)		Urine production (ml/day)	
	Erythritol	Sucrose	Erythritol	Sucrose	Erythritol	Sucrose
1	70.7	70.6	2349	2461	1605	2240
2	97.3	97.2	3780	3270	3410	2793
3	71.0	70.4	2152	2530	3285	3000
4	80.1	79.7	2444	2600	3368	2920
5	73.9	73.8	1600	1152	2305	1738
6	76.9	77.8	2554	1984	2800	2193
7	70.8	71.1	1506	2898	2370	2550
8	92.9	93.8	5580	5382	5955	6023
9	93.3	94.1	1834	1590	2145	1648
10	70.2	69.5	2480	2180	2458	2445
11	85.2	85.0	3152	3556	5115	5245
12	65.4	65.8	1512	1620	1878	1585
Mean SD (n)	79.0 ± 10.7 (12)	79.1 ± 10.9 (12)	2579 ± 1162 (12)	2602 ± 1122 (12)	3058 ± 1304 (12)	2865 ± 1387 (12)

Note. Values are means of five measurements (on Days 3–7 of each treatment period).

sure values were within the normal physiological range. Statistical analysis of the data did not reveal a treatment-related effect (Table 3).

The liquid intake differed considerably between individuals but not between treatments (Table 4). In comparison to usual amounts of liquid intake, the volumes recorded in the present study were high (see "Discussion" for references).

During the erythritol test period, erythritol was detected in the urine of all subjects on all days. The lowest value on any of the 48 subject-days was 38.4 g/day, corresponding to 54.3% of the nominal ingested dose. On average of all subject-days, the erythritol excretion was 62.4 g/day, corresponding to about 78.0% of the nominal ingested dose. Since erythritol absorption is estimated at about 80–90% from other studies, this value documents good compliance with the test regimes of the present subjects.

Urine production was increased during the erythritol period by about 7% (difference not statistically significant, $P = 0.08$) (Tables 4 and 5). The urinary concentrations (in mmol/liter) of sodium ($P = 0.07$), potassium ($P = 0.04$), chloride ($P = 0.02$), and creatinine ($P = 0.06$) tended to be lower during the erythritol treatment period (data not shown). Together, these observations point to a slight diuretic effect of erythritol which, however, was of borderline statistical significance under the conditions of the present study. Urinary pH was not different between the two treatment periods (Table 5).

Urinary osmolality and the hourly urinary output of osmotically active solutes were significantly increased during the erythritol test period (Table 5). The observed increase of 576 mOsm/24 hr corresponds well

to the expected increase calculated from the erythritol output (62.4 g/24 hr = 511 mOsm/24 hr).

The urinary output of creatinine, urea, Na^+ , K^+ , Cl^- , P_i , and citrate was not influenced by erythritol treatment (Table 5). Among the urinary electrolytes examined only calcium was significantly increased during the erythritol treatment ($P \leq 0.04$). However, in absolute terms, this increase was small (4%). The urinary NAG-, $\beta_2\text{M}$ -, and albumin outputs were significantly increased during the erythritol test period (Table 5). However, these increases, which were significant also after normalization for creatinine excretion, were numerically small and all values remained well within the physiological range (for NAG and $\beta_2\text{M}$ see Figs. 2 and 3, respectively).

The participants' reports on the frequency, appearance, and quantity of their feces reveal that the frequency of stool did not differ between the treatments. However, the appearance was judged slightly more often as being "softer than usual" during the erythritol treatment than during the sucrose treatment (14/60 vs 8/60 observations). On the other hand, the quantity of stool was more often rated as "less than usual" during the erythritol treatment than the sucrose treatment (13/60 vs 5/60 observations) (Table 6). The subjective judgements of the frequency and quantity of urine production did not differ between the two treatment periods (Table 6).

Gastrointestinal side effects such as flatulence, bloated feeling, and sensation of fullness were reported by six subjects on a total of 10 occasions during the erythritol test period and 13 occasions during the sucrose test period. Except for headache, which was reported by one subject on Day 3 of the erythritol period

TABLE 5
Urine Production and Urinary Parameters of 12 Healthy Male Volunteers Ingesting Erythritol or Sucrose at up to 1 g/kg bw/Day for Periods of 1 Week

Urinary parameter	Treatment	
	Erythritol	Sucrose
Volume (ml/hr)	127 ± 54	119 ± 58
pH	6.1 ± 0.3	6.1 ± 0.3
Osmolality		
mOsm/kg	689 ± 169***	559 ± 160
mOsm/hr	75 ± 12***	51 ± 6
Creatinine (mmol/hr)	0.79 ± 0.14	0.80 ± 0.12
Urea (mmol/hr)	21 ± 3	20 ± 2
mmol/mmol creatinine	26.5 ± 2.8 ^a	25.0 ± 4.0
Sodium (mmol/hr)	10.1 ± 1.8	10.3 ± 1.8
mmol/mmol creatinine	13.1 ± 1.6	13.0 ± 1.9
Potassium (mmol/hr)	3.9 ± 0.7	3.9 ± 0.5
mmol/mmol creatinine	5.0 ± 1.0	4.9 ± 0.9
Calcium (mmol/hr)	0.26 ± 0.05*	0.25 ± 0.06
mmol/mmol creatinine	0.35 ± 0.11***	0.32 ± 0.11
Chloride (mmol/hr)	9.6 ± 1.6	10.0 ± 1.5
mmol/mmol creatinine	12.3 ± 1.5	12.6 ± 1.7
Phosphate (mmol/hr)	1.63 ± 0.31	1.53 ± 0.26
mmol/mmol creatinine	2.09 ± 0.36*	1.94 ± 0.34
Citrate (mg/hr)	23 ± 6	23 ± 8
mg/mmol creatinine	30.6 ± 11.6	30.7 ± 13.8
NAG (IU/hr)	0.25 ± 0.05***	0.20 ± 0.04
IU/mmol creatinine	0.34 ± 0.09***	0.26 ± 0.07
μ-Albumin (mg/hr)	0.32 ± 0.10 ^a	0.31 ± 0.18
mg/mmol creatinine	0.42 ± 0.13 ^a	0.39 ± 0.25
β ₂ -Microglobulin (μg/hr)	5.4 ± 1.2*** ^a	4.3 ± 0.8
μg/mmol creatinine	7.0 ± 1.6*** ^a	5.4 ± 1.2

Note. Values are means ± SD ($n = 12$ subjects). The individual values were calculated as the time-weighted mean of each subject's 24 urine samples (four 24-hr periods of 6 samples each). Levels of statistical significance for the test of treatment difference: * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ (repeated-measures ANOVA (four 24-hr values/subject/treatment)).

^a Statistical test applied on transformed values (inverse normal scores of ranks).

and on Days 4 and 5 of the sucrose period, no other symptoms of illness or potential intolerance to the treatments were noted. The subjects' feelings of hunger/appetite and thirst and their desire for sweet or salty foods also remained unaffected by the erythritol treatment.

DISCUSSION

The present study was conducted in order to examine the tolerance of the human intestinal and urinary system to repeated oral doses of erythritol. By quantitat-

ing the urinary erythritol output, additional information about the fractional intestinal absorption of this polyol was obtained.

Intestinal Tolerance

It is well established that the consumption of excessive amounts of polyols and slowly digestible carbohydrates (e.g., lactose) can provoke undesirable intestinal side effects such as flatulence, abdominal cramps, laxation, and—in extreme cases—watery diarrhea. Some of these symptoms are the result of osmotic effects, and

TABLE 6
Subjective Assessment of Stool and Urine Production by 12 Healthy Male Volunteers Ingesting Erythritol or Sucrose at up to 1 g/kg bw/Day for Periods of 1 Week Each

Observations	Day:	Feces										Urine														
		Erythritol					Sucrose					Erythritol					Sucrose									
		3	4	5	6	7	3	4	5	6	7	3	4	5	6	7	3	4	5	6	7					
Frequency																										
Less than usual		2	1	1	2	1	1	2	0	1	1	1	2	1	2	0	1	1	1	1	1	0				
Normal		10	11	10	10	11	11	10	11	11	11	8	8	9	9	10	10	9	9	9	10	11				
More than usual		0	0	1	0	0	0	0	0	0	0	3	2	2	1	2	1	2	2	2	1	1				
A lot more than usual		0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0				
Appearance																										
Tighter than usual		2	1	2	0	1	1	1	0	1	1															
Normal		6	8	6	10	9	10	9	9	9	10															
Softer than usual		4	3	4	1	2	1	2	2	2	1															
A lot softer than usual		0	0	0	1	0	0	0	1	0	0															
Quantity																										
Less than usual		2	3	2	3	3	0	3	1	0	1	2	1	2	2	1	0	2	1	0	0	1				
Normal		9	9	10	8	9	12	9	10	12	11	8	8	7	7	8	9	9	8	11	9					
More than usual		1	0	0	1	0	0	0	0	0	0	2	3	3	3	3	3	1	2	1	2					
A lot more than usual		0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0				

others are the result of the fermentative degradation of these compounds in the colon. Numerous human tolerance studies have shown that the incidence and severity of these intestinal side effects and their threshold dose depend upon the particular polyol consumed, the mode of its ingestion, the existence of a previous adaptation period, and the individual susceptibility for this kind of effects.

Under the conditions of the present study, erythritol at a daily dose of 1 g/kg bw was tolerated without any untoward intestinal side effects by all subjects. In another study of almost identical design, the ingestion of xylitol at the same dose induced slight laxation in 2 out of 12 subjects (Bär, 1985). When sorbitol was ingested with water in two daily doses (after breakfast and dinner), 11 out of 21 subjects experienced unacceptable intestinal side effects at a daily dose of 60 g which also corresponds to about 1 g/kg bw (Patil *et al.*, 1987).

Taken together, these data support the concept of an increasing intestinal tolerance of polyols and carbohydrates with increasing small-intestinal absorption. The present observation of a good intestinal tolerance of erythritol is in line with corresponding results of other trials in which the administered single doses were even higher than the amounts which were consumed per eating occasion during the present study (Hiele *et al.*, 1993; Noda *et al.*, 1994).

Absorption and Urinary Excretion of Erythritol

On average the urinary excretion of erythritol (and thus its intestinal absorption) accounted for 78.0% of

the nominally ingested dose. This value corresponds well with the 80–90% range reported for erythritol absorption from metabolic studies in human volunteers (Bornet *et al.*, 1992; Hiele *et al.*, 1993; Noda *et al.*, 1994). If calculated for each of the 12 participants separately, the erythritol excretion varied between 61.0 and 88.0% of the ingested dose. In 11 subjects, the fractional erythritol excretion exceeded 70%.

Examination of the diurnal variation of the erythritol output (expressed in g/hr) revealed a similar pattern for all subjects with highest excretion rates of between about 4 and 7 g/hr in the afternoon and lowest excretion rates of between 0.5 and 2 g/hr in the overnight samples. The data for a typical subject are presented in Fig. 1.

Tolerance of the Urinary System

In the present study, the tolerance of the urinary system to the excretion of substantial amounts of erythritol was examined with regard to effects on diuresis, electrolyte excretion, and parameters related to the glomerular and tubular function of the nephron (urinary albumin, β_2 M, NAG).

Under the conditions of the present study, the ingestion of erythritol at 1 g/kg bw/day was not associated with a significant increase of urine production. The subjective judgements of the frequency and quantity of urine production and of thirst also did not differ significantly between the treatment periods with erythritol or sucrose consumption. An absence of a significant diuretic response was also observed in a different study in which a single erythritol dose of 0.3 g/kg bw was administered

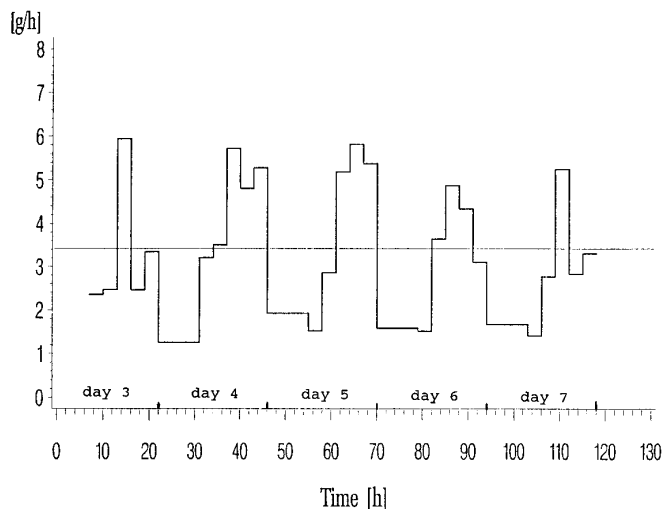


FIG. 1. Urinary output of erythritol (g/h) of one subject consuming erythritol at 1 g/kg bw/day. Subject was No. 2. Time = 0 h corresponds to Monday 00:00. After an adaptation period on Saturday and Sunday, treatment at a dose of 1 g/kg bw started with breakfast on Monday morning (08:00). The last sample was collected on Friday evening (22:00). The horizontal line denotes the average.

(Noda *et al.*, 1994). Nevertheless, a slight diuretic effect of the erythritol treatment is suggested by decreased urinary concentrations of creatinine and several electrolytes (Na^+ , K^+ , Cl^-), and the observation of thirst by one subject on each day of the erythritol period. It is possible that in most participants of the present study a rather high intake of liquid (due to hot weather) masked a mild diuretic response to erythritol. Indeed, 10 out of 12 subjects drank more than the reported average liquid intake of 1.8 liters/day (Houghton and Langlais, 1989; cited in Bär and Würtzen, 1990).

Except for calcium and perhaps phosphate, the urinary excretion of other electrolytes measured was not affected by the erythritol treatment (Table 5). This is noteworthy because the administration of many diuretics (including osmotic diuretics) may result in increased sodium and potassium excretion. Lack of an effect of erythritol on electrolyte balance was also reported from another study in which the ingestion of a single dose of erythritol at 0.3 g/kg bw did not influence the urine and serum levels of Na^+ , K^+ , and Cl^- (Noda *et al.*, 1994).

The increase in calcium excretion, while significant, was numerically very small (Table 5). Moreover, only 7 out of 12 subjects exhibited a higher calcium excretion during the erythritol period.

The urinary excretion of albumin, which is increased under conditions of an impaired glomerular permselectivity or tubular reabsorption of proteins, was slightly increased during the erythritol treatment (Table 5). However, this increase appears to lack clinical relevance since it was numerically very small and since the daily albumin excretion was well within the range

of physiological values in all subjects on all days during either of the two treatments (data not shown).

The urinary excretion of $\beta_2\text{M}$ is increased under conditions of impaired tubular reabsorption of ultrafiltered, low-molecular-weight proteins (Weise *et al.*, 1981). In the present study, a 25% increase of the urinary $\beta_2\text{M}$ output was observed during the erythritol treatment. Despite this statistically significant increase, the values were still well within the limits of normal reference values (Wibell, 1985; Alt *et al.*, 1981). It also should be noted that similar or higher increases have been seen after intake of high amounts of sugar, during pregnancy, in hyperthyroid patients, or in marathon runners after exercise, i.e., conditions that are not normally associated with renal disease (Li *et al.*, 1986; Lew *et al.*, 1991). The observed increase of $\beta_2\text{M}$ is also small in comparison to the 45–60% differences of $\beta_2\text{M}$ excretion between healthy subjects in supine and upright positions (van Acker, 1993).

A quantitatively and qualitatively similar increase as noted for $\beta_2\text{M}$ was observed for urinary NAG. Interestingly, the excretion profiles of NAG and $\beta_2\text{M}$ also exhibited a certain coordinacy during both treatment periods. The hourly NAG output was usually lowest in the samples produced overnight. In a few samples, NAG and $\beta_2\text{M}$ were elevated concomitantly by more than 100% above the means. Such isolated increases were seen during both the erythritol and sucrose period but in several subjects they were higher during the latter. The approximate margins within which a subject's NAG and $\beta_2\text{M}$ excretions fluctuate remained stable during the entire study and were not affected by consumption of erythritol. This is illustrated in Figs. 2 and 3 which present the NAG and $\beta_2\text{M}$ excretion profiles of those two subjects who exhibited the highest and lowest excretions of NAG and $\beta_2\text{M}$ during the erythritol and sucrose periods, respectively. The example of these two subjects as well as the data of all other participants indicate that the small increases of NAG and $\beta_2\text{M}$ excretions during the erythritol period do not exceed the physiological range.

CONCLUSIONS

The results of the present study demonstrate that the repeated ingestion of erythritol at a daily dose of 1 g/kg bw is well tolerated. Under the conditions of the present study gastrointestinal side effects did not occur more frequently with erythritol than with sucrose. The liquid intake and urine production also remained unchanged. The excretion in the urine of about 78% of ingested erythritol led to a higher urinary osmolality but did not influence the 24-hr output of creatinine, urea, or electrolytes (Na^+ , K^+ , Cl^- , P_i , citrate). The excretion of calcium was slightly higher during the erythritol test period but in absolute terms this increase was small. The urinary excretions of albumin,

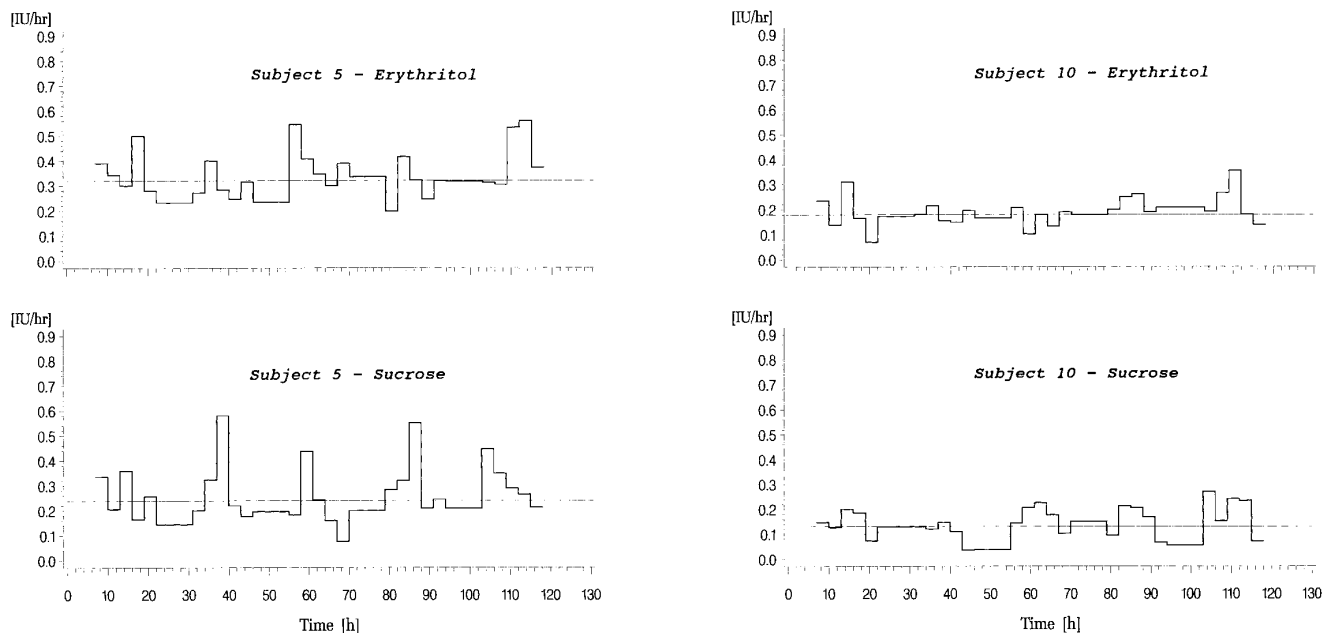


FIG. 2. Urinary excretion of *N*-acetylglucosaminidase during ingestion of sucrose or erythritol at 1 g/kg bw for 5 days. Of the 12 subjects studied, subject 5 had the highest mean *N*-acetylglucosaminidase excretion during the erythritol period and subject 10 the lowest mean *N*-acetylglucosaminidase excretion during the sucrose period. The horizontal line denotes the average.

β_2 M, and NAG were higher during the erythritol test period but they were still well within the physiological range. None of the observed urinary changes became

more pronounced with increasing duration of the erythritol treatment. In conclusion, erythritol was well tolerated and without any evidence of adverse effects.

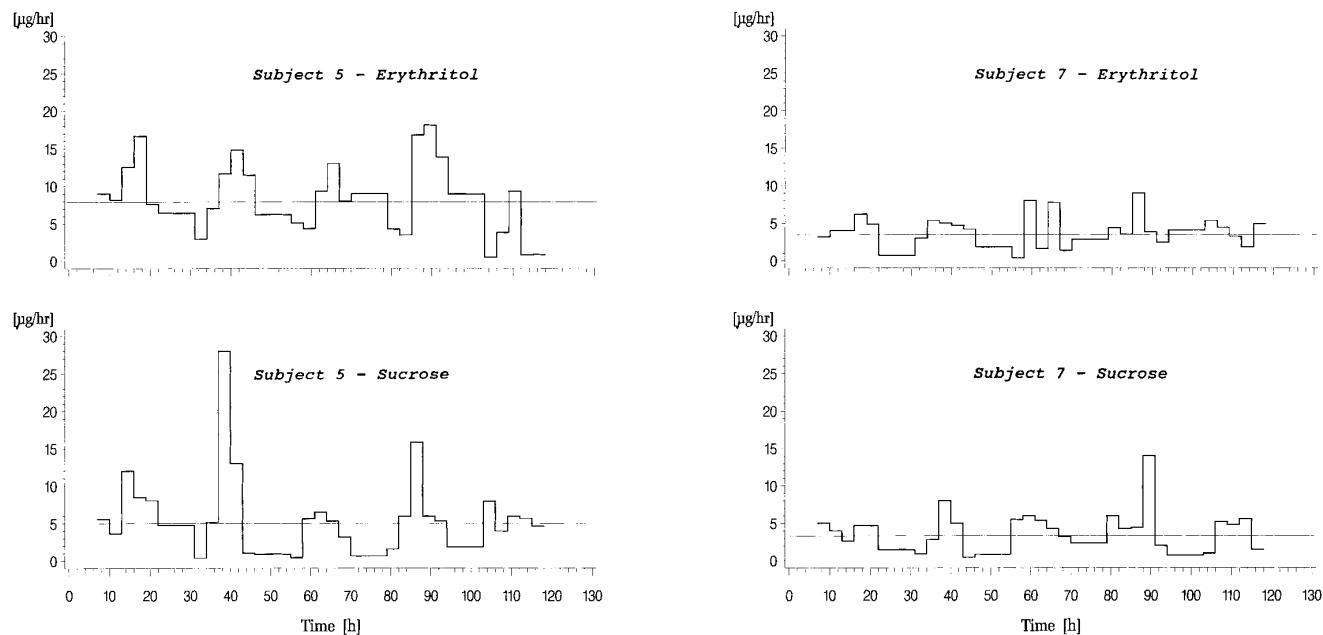


FIG. 3. Urinary excretion of β_2 M during ingestion of sucrose or erythritol at 1 g/kg bw for 5 days. Of the 12 subjects studied, subject 5 had the highest mean β_2 M excretion during the erythritol period and subject 7 the lowest mean β_2 M excretion during the sucrose period. The horizontal line denotes the average.

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