

Plasma and Urine Kinetics of Erythritol after Oral Ingestion by Healthy Humans

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The plasma and urine kinetics of erythritol and the effect of erythritol on plasma glucose and insulin levels were studied in human volunteers administered a single oral dose of 1 g erythritol/kg body wt. The plasma level of erythritol increased during the first 30 to 40 min, reaching a maximum value of approximately 2.2 mg/ml after 90 min. Plasma levels of erythritol then declined gradually to approximately 1.5 to 1.7 mg/ml at the end of the 3-hr sampling period. An average of 30% of the ingested amount of erythritol was excreted unchanged in the urine during the first 3 hr. Total urinary excretion increased to 78% after 24 hr. Renal clearance of erythritol was approximately half that of creatinine, indicating tubular reabsorption of erythritol by the kidney. Mean plasma glucose and insulin levels, measured for up to 3 hr after ingestion, were unaffected by erythritol. The results of this study indicate that erythritol was readily absorbed following oral administration and was excreted unchanged in the urine. Less than 20% of erythritol remained unabsorbed and was available for colonic fermentation and potential production of short-chain fatty acids. Its caloric value was estimated to be ≤ 0.4 kcal/g. © 1996

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INTRODUCTION

Erythritol is a sugar alcohol which, following ingestion, is rapidly absorbed from the small intestine due to its low molecular weight. It is not metabolized by the human body and is excreted unchanged in the urine (Oku and Noda, 1990; Hiele *et al.*, 1993). Due to its good absorption, only a small fraction of ingested erythritol reaches the large intestine where it is available to undergo fermentation by the gut microflora (Oku and Noda, 1990; INRA, unpublished report). The low amount of erythritol reaching the lower intestine reduces its potential conversion to useable energy sources and prevents osmotic diarrhea and flatulence. In addition,

the absence of systemic metabolism of erythritol means that it has limited potential to induce changes in plasma glucose and insulin levels. Together, these properties suggest that erythritol may be used advantageously in special foods for people with diabetes.

The aim of the current study was to determine the plasma and urine kinetics of erythritol and examine its metabolic effect on plasma glucose and insulin levels after ingestion of a single oral dose.

MATERIALS AND METHODS

Subjects

Six volunteers, consisting of three males and three females aged 24 to 43 years (mean 32.67 ± 6.8 years) with a body mass index (BMI, 22 ± 1.65 ; range = 19–24), were studied. No subjects were included in the study who had fasting blood sugar levels above 5.5 mmol/liter, were pregnant, had diabetes mellitus, or were HIV positive. All subjects participated in the study after their informed consent was obtained. The study protocol was approved by the ethics committee of Hôpital Hotel-Dieu.

Materials

Erythritol (99.9% purity) was provided by Cerestar, Belgium.

Study Design

Following an overnight fast, all subjects ingested a single oral dose of 1 g erythritol/kg body wt dissolved in 250 ml of water. The total dose administered to each subject ranged from 56 to 78 g, depending on the body weight of the individual. Fifteen minutes prior to erythritol administration and every 30 min during the period from 0 to 3 hr post-ingestion, blood samples were collected for analysis of plasma glucose and insulin levels. Blood samples also were collected for analysis of plasma erythritol levels every 5 min during the period

TABLE 1
Total Amount of Erythritol Ingested by
Six Healthy Subjects

Total amount of ingested erythritol (g)							
S1 ^a	S2	S3	S4	S5	S6	Mean	SEM ^b
60	56	58	78	64	68	64	3.3

^a Indicates number of subject.

^b SEM, standard error of the mean.

from 0 to 15 min postingestion, every 15 min during the period from 15 min to 1 hr postingestion, and every 30 min during the period from 1 to 3 hr postingestion. A blood sample also was taken prior to erythritol ingestion for the determination of plasma creatinine levels.

At 30 min and 1, 2, and 3 hr postingestion, urine was collected, its volume was measured, and erythritol and creatinine concentrations were determined. Over the next 21 hr, total urine output was measured. Follow-up medical examinations were performed 24 hr after erythritol administration.

Urine samples were stored at -20°C for 5 weeks prior to erythritol determinations. Similarly, plasma samples were stored at -20°C for 4 to 5 weeks prior to erythritol and insulin determinations. Plasma glucose determinations were conducted immediately after collection.

Determinations

Plasma erythritol concentration. The plasma erythritol concentration was determined using a high-pressure liquid chromatograph (HPLC) method with 1,3-butanediol as an internal standard (IS). 1,3-Butanediol has similar chromatographic properties to erythritol and was added to plasma samples before deproteiniza-

tion. A 1/100 dilute solution of IS was originally prepared and the area under the HPLC curve measured under the conditions of the assay.

Plasma samples were centrifuged and analyzed in triplicate. One milliliter of the 1/100 dilution of IS was mixed with 3 ml of centrifuged plasma sample before deproteinization. Deproteinization was performed by mixing 3 ml of ice-cold perchloric acid (0.6 mol/liter) with the IS/plasma sample mixture in a centrifuge tube. After centrifugation, 1 ml of potassium carbonate solution (0.75 mol/liter) was mixed with 3 ml of supernatant, put in an ice bath for 3 min, then centrifuged. The supernatant was immediately frozen at -20°C for HPLC analysis at a later time. After thawing, the samples were centrifuged and the supernatant was decanted and put into HPLC vials. Erythritol was measured by means of HPLC using a Waters HPLC Solvent Delivery System M45 with a Waters HPLC Differential Refractive Index Detector R401 (Millipore Corp., Milford, MA). A Shodex Ionpack Column KC811 with an internal diameter of 8 mm and a length of 300 mm was used. The injected sample volume was $5\ \mu\text{l}$. The column operating temperature was 75°C and the flow rate was 1 ml/min. HPLC-grade water containing 0.0018 H_2SO_4 was used as the eluent.

Sample preparation and HPLC processing procedures, such as adding the IS before the deproteinization step, were designed to avoid manipulation errors. The recovery of the IS in the final sample was calculated based on the original amount of IS added to the sample. The percentage recovery was applied to the analytically determined erythritol levels to compensate for manipulation errors.

A dilution factor of 2.60 was used to account for the dilution of samples which occurred during plasma separation and protein precipitation. Results were expressed as erythritol concentration (g/liter).

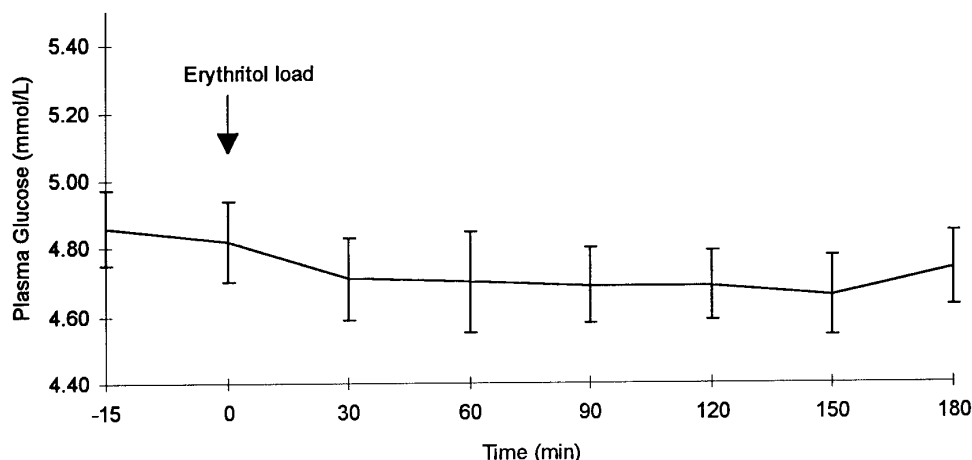


FIG. 1. Mean plasma glucose concentration in six subjects following ingestion of a single oral dose of 1 g erythritol/kg body wt. Error bars indicate standard error of the mean (SEM).

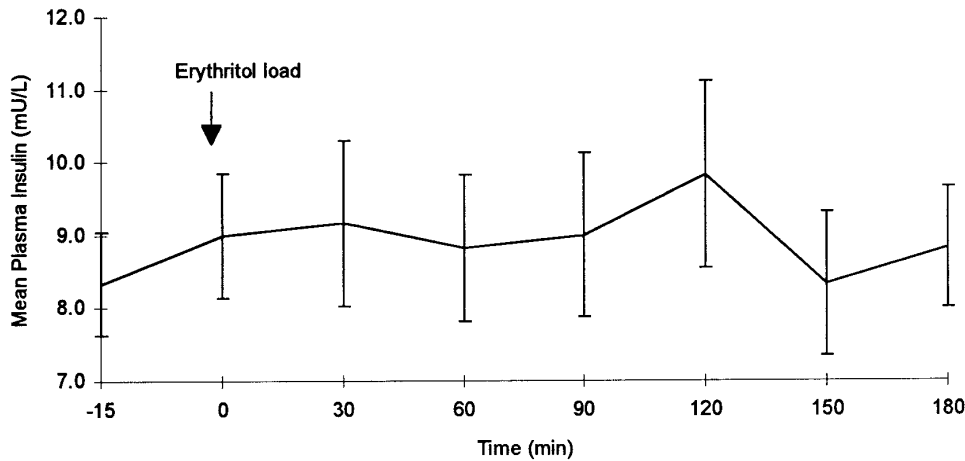


FIG. 2. Mean plasma insulin concentration in six subjects following ingestion of a single oral dose of 1 g erythritol/kg body wt. Error bars indicate standard error of the mean (SEM).

Urine erythritol concentration. Urine samples were frozen and stored at -20°C for HPLC determination of erythritol content at a later time. After thawing, urine samples were rehomogenized and filtered through a $0.45\text{-}\mu\text{m}$ filter. Samples of 0.5 ml were mixed with 0.25 ml of the IS before being placed in HPLC vials. The HPLC method was the same as described for the plasma erythritol determinations. Urine erythritol concentration was expressed as g/liter and erythritol output as g/min.

Erythritol clearance (expressed as ml/min) was calculated as the ratio of erythritol excreted in urine during the 120- to 180-min period following ingestion to the mean plasma erythritol concentration during the same period. Plasma glucose levels (expressed in mmol/liter) were measured by a glucose oxidase method using the Beckman Analyzer II. Plasma insulin levels (ex-

pressed as mU/liter) were determined by a radioimmunoassay using dextrancharcoal separation (intraassay variability = 6%). Plasma and urine creatinine levels (expressed as $\mu\text{mol/liter}$ and mmol/liter, respectively) were measured using a kinetic colorimetric assay (Synchron CX3, Beckman). Creatinine clearance (expressed as ml/min) was calculated as the ratio of urine creatinine excreted for the 120- to 180-min period to the fasting plasma creatinine level.

RESULTS

Total erythritol intakes by the individual subjects are shown in Table 1. Intake ranged from 56 to 78 g per person, with a mean value of 64 g. Four of six subjects (three females and one male) described gastrointestinal symptoms at the 24-hr follow-up examina-

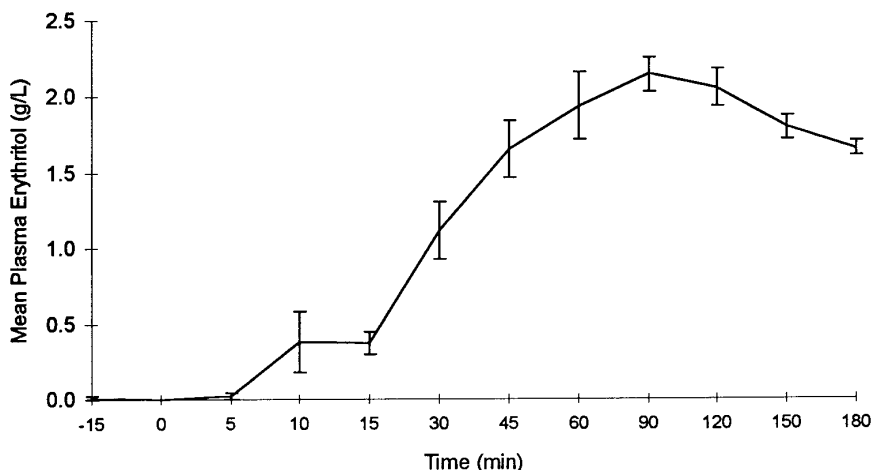


FIG. 3. Mean plasma erythritol concentration in six subjects following ingestion of a single oral dose of 1 g erythritol/kg body wt. Error bars indicate standard error of the mean (SEM).

TABLE 2
Fractional Urine Volume in Six Subjects at Various Time Intervals Following Ingestion of 1 g Erythritol/kg Body Wt

Time (min)	Fractional urine volume (liters)						Mean	SEM ^b
	S1 ^a	S2	S3	S4	S5	S6		
0-30	0.06	0.08	0.06	0.04	0.04	0.11	0.07	0.01
30-60	0.07	0.07	0.10	0.06	0.06	0.12	0.08	0.01
60-120	0.22	0.17	0.15	0.19	0.14	0.25	0.19	0.02
120-180	0.18	0.15	0.17	0.18	0.13	0.19	0.16	0.01
180-1440	1.12	1.00	2.66	1.10	1.75	1.05	1.45	0.27
0-180	0.53	0.46	0.48	0.46	0.38	0.67	0.50	0.05
0-1440	1.65	1.46	3.14	1.56	2.13	1.72	1.94	0.26

^a Indicates number of subject.

^b SEM, standard error of the mean.

tion. Two subjects reported diarrhea while the others reported abdominal cramping, discomfort, and flatulence.

Plasma glucose levels are shown in Fig. 1. Levels for insulin are shown in Fig. 2. The data indicate that neither plasma glucose nor plasma insulin was affected by the ingestion of erythritol. Mean plasma erythritol levels are depicted in Fig. 3. An increase in plasma erythritol levels was observed over the first 30 to 40 min following ingestion, reaching a mean maximal value of approximately 2.2 mg/ml after 90 min. Two individuals (subjects 1 and 5) showed a plasma erythritol concentration plateau of approximately 1.8 mg/ml after 90 min. The other four individuals showed a more pronounced elevation of plasma erythritol (approximately 2.3 mg/ml) followed by a gradual decline. All subjects showed a tendency toward declining plasma erythritol levels 120 min following ingestion. By 180 min, comparable plasma concentrations (1.5 to 1.7 mg/ml) were reached in all subjects. Urinary volume following erythritol ingestion is shown in Table 2. Mean urinary erythritol concentra-

tions are shown in Fig. 4. These data indicate that urine volume and erythritol levels reached a maximum during the period from 60 to 120 min after ingestion. Cumulative amounts of erythritol excreted in the urine for each period are shown in Fig. 5. The cumulative erythritol urinary excretion as a percentage of total ingested erythritol is shown in Table 3. On average, 30% of ingested erythritol was excreted during the first 180 min. After 24 hr, approximately 78% of the total amount ingested was recovered in the urine. Individual values for erythritol and creatinine clearance for the period from ingestion to 180 min after ingestion are shown in Table 4. The mean erythritol clearance for the six subjects was 62.0 ± 2.8 ml/min. During the same period, creatinine clearance was 120.2 ± 12.3 ml/min.

DISCUSSION

The results of the current study demonstrate that erythritol undergoes rapid absorption by the small intestine following single oral administration of 1 g

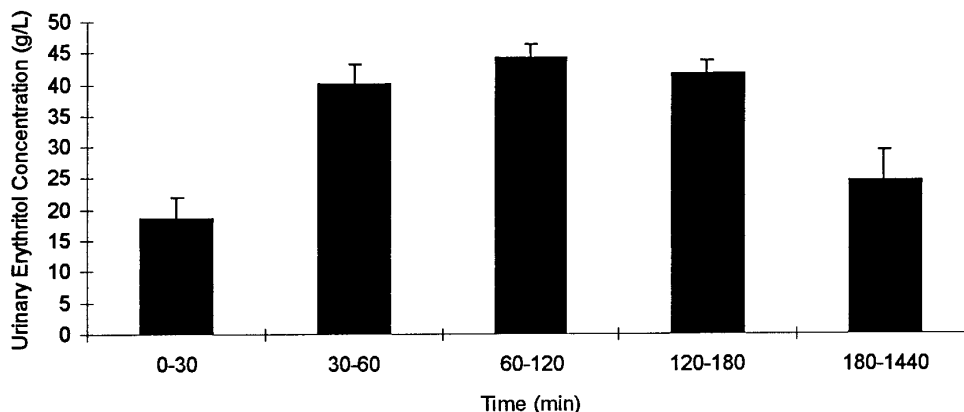


FIG. 4. Mean urinary erythritol concentrations in six subjects at various time intervals following ingestion of 1 g erythritol/kg body wt. Error bars indicate standard error of the mean (SEM).

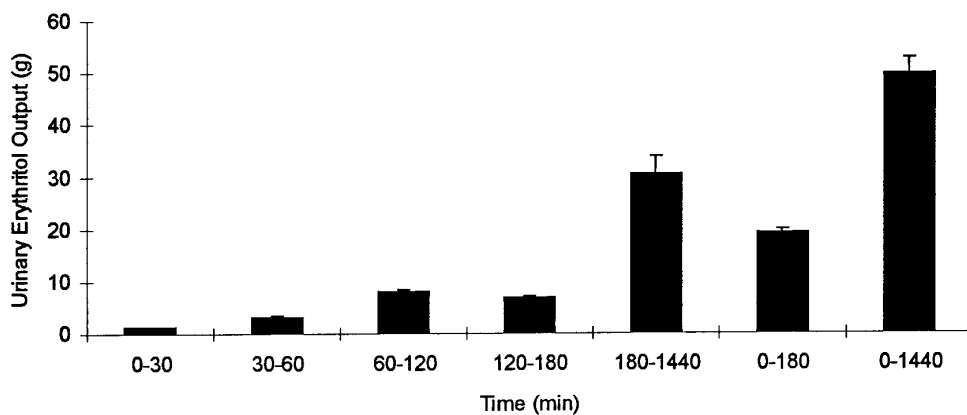


FIG. 5. Mean cumulative urinary erythritol output in six subjects at various time intervals following ingestion of 1 g erythritol/kg body wt. Error bars indicate standard error of the mean (SEM).

erythritol/kg body wt/day. Erythritol appeared in both plasma and urine within a few minutes of dosing. Plasma levels increased for up to 90 min after ingestion to reach a plateau after approximately 120 min, indicating a temporary balance between absorption and excretion. After 24 hr, close to 80% of the total amount of ingested erythritol was recovered in the urine. These findings compare well with the results of previous metabolic studies in humans in which erythritol absorption was reported to range from 80 to 90% (Hiele *et al.*, 1993; Noda *et al.*, 1994). Renal clearance of erythritol was 62.03 mg/min, approximately half the rate for creatinine, indicating tubular reabsorption of erythritol by the kidney. The relative renal excretion of erythritol may be compared to that of mannitol for which the ratio of excretion to that of creatinine is about 1 (Smith *et al.*, 1940). Plasma and urine measurements of erythritol indicate a lack of metabolic change and no effect on glucose or insulin parameters. This indicates an overall inertness.

Based on the high degree of intestinal absorption of erythritol, only small amounts appear to reach the

colon. In this study, less than 20% of orally ingested erythritol would potentially have been available for fermentation by colonic microorganisms. In *in vitro* (INRA, unpublished report) or *in vivo* studies with humans (Hiele *et al.*, 1993), erythritol is not fermented by gut microflora. Nevertheless, considering the potential energy value of short-chain fatty acids, the caloric value of erythritol was estimated to be ≤ 0.4 kcal/g. The moderate gastrointestinal side effects, which occurred in a few subjects, were considered to be due to the extremely high liquid erythritol load (~ 60 g) used. These gastrointestinal effects were not observed when similar doses of erythritol were incorporated into food (Bornet *et al.*, 1996).

The present study demonstrates that substantial amounts of erythritol are rapidly absorbed from the gastrointestinal tract following oral administration. Excretion also appears to occur rapidly, with only unchanged erythritol appearing in the urine. Erythritol did not induce clinically significant changes in either plasma glucose or insulin concentrations despite being absorbed in large amounts. Based on these results, it can be concluded that erythritol has

TABLE 3
Cumulative Urinary Excretion of Erythritol, as a Percentage of Total Amount Ingested, in Six Subjects at Various Time Intervals Following Ingestion of 1 g Erythritol/kg Body Weight

Time (min)	Percentage of ingested erythritol dose in urine (%)						Mean	SEM ^b
	S1 ^a	S2	S3	S4	S5	S6		
0-30	1	2	3	1	2	2	2	0
0-60	5	7	11	4	7	8	7	1
0-120	20	21	23	15	18	22	20	1
0-180	31	33	36	24	28	31	30	2
0-1440	99	83	81	75	60	72	78	5

^a Indicates number of subject.

^b SEM, standard error of the mean.

TABLE 4
Comparative Urinary Erythritol and Creatinine Clearance in Six Subjects 120–180 min
after Ingestion of 1 g Erythritol/kg Body Wt

	Clearance (ml/min)						Mean	SEM ^b
	S1 ^a	S2	S3	S4	S5	S6		
Erythritol clearance	67.1	56.0	71.6	61.6	62.7	53.3	62.0	2.8
Creatinine clearance	131.9	97.3	174.0	120.7	104.0	93.4	120.2	12.3

^a Indicates number of subject.

^b SEM, standard error of the mean.

considerable potential as a low-calorie sugar substitute for use in food items for consumption by humans, including people with diabetes.

REFERENCES

- Bornet, F., Blayo, A., and Slama, G. (1996). Gastrointestinal response and plasma and urine determinations in human subjects given erythritol. *Regul. Toxicol. Pharmacol.* **24**(Suppl.), 000–000.
- Hiele, M., Ghos, Y., Rutgeers, P., and Vantrapen, G. (1993). Metabolism of erythritol in humans: Comparisons with glucose and lactitol. *Br. J. Nutr.* **69**, 169–176.
- INRA, unpublished report. *In vitro* fermentation of indigestible carbohydrates by human faecal flora. Internal Report, INRA, Contract #34.92.020.
- Noda, K., Nakayama, K., and Oku, T. (1994). Serum glucose and insulin levels and erythritol balance after oral administration of erythritol in healthy subjects. *Eur. J. Clin. Nutr.* **48**, 286–292.
- Oku, T., and Noda, K. (1990). Erythritol balance study and estimation of metabolisable energy of erythritol. In *Caloric Evaluation of Carbohydrates* (N. Hosoya, Ed.). Proceedings of the International Symposium on Caloric Evaluation of Carbohydrates, pp. 65–75.
- Smith, W. W., Finkelstein, N., and Smith, H. W. (1940). Renal excretion of hexitols (sorbitol, mannitol and dulcitol) and their derivatives (sorbitan, isomannide, and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J. Biol. Chem.* **135**, 231–250.