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Lactitol: Gastrointestinal Absorption and Effect on Blood Lactate in Healthy Volunteers and Patients with Cirrhosis

J. Metzger[1], C. Chollet[2], M. Wermeille[2], J. Biollaz[3], J. B. Llull[2], and B. H. Lauterburg[1]

[1] Department of Clinical Pharmacology, University of Bern, Bern,
[2] Zyma, Nyon, and [3] Division of Clinical Pharmacology, University of Lausanne, Lausanne, Switzerland

Summary. The gastrointestinal absorption of lactitol has been studied in 6 healthy volunteers and 8 patients with cirrhosis.

Following administration of lactitol 0.5 g/kg, no lactitol was found in serum. The urinary excretion of lactitol over 24 h ranged from 0.1 to 1.4% of the administered dose (0.46% in cirrhotics and 0.35% in healthy volunteers). Blood D- and L-lactate and plasma glucose did not increase following lactitol.

The data indicate that lactitol was poorly absorbed from the gastrointestinal tract in healthy volunteers and patients with cirrhosis, and that the disaccharide did not disturb glucose or lactate homeostasis.

Key words: lactitol; gastrointestinal absorption, blood lactate, cirrhosis, metabolic effects

Recently, lactitol, 4-beta-D-galactopyranosyl-D-sorbitol, has been introduced for the treatment of porto-systemic encephalopathy [1-4]. Like lactulose, which has been successfully used for the management of this often disabling condition for a number of years [5], lactitol is a disaccharide, which is metabolized by intestinal bacteria but not by endogenous hydrolases in the gastro-intestinal mucosa of man [6]. In contrast to lactulose, which is a very sweet syrup, lactitol is more palatable and is available as a powder suitable for sweetening beverages [7]. It may prove more acceptable to patients with encephalopathy requiring chronic treatment, and because of its better palatability it may become an important alternative in the management of constipation.

Since the biological effects of the compound depend on its metabolism by intestinal (i.e. mainly colonic) bacteria, lactitol should reach the colon intact and should not be absorbed from the gastrointestinal tract. To quantitate the gastrointestinal absorption and bioavailability of lactitol, its serum concentration and urinary excretion were measured in healthy volunteers and cirrhotic patients in whom handling of the compound and its metabolites by the gastrointestinal tract and by the liver might be altered due to portal hypertension and decreased hepatic function. In rats, more than 85% of an intravenous dose of lactitol is excreted unchanged in urine (unpublished observation). Therefore, the urinary excretion of lactitol may be considered to reflect its bioavailability.

Subjects and Methods

Normal Volunteers

Six (5 male and 1 female) healthy volunteers, aged 19-38 years, were studied. Physical examination and routine laboratory tests (serum creatinine, alkaline phosphatase, aspartate amino transferase, bilirubin, white blood count and haemoglobin) were all within normal limits. The subjects were not taking any medication and did not drink more than 25 g ethanol per day.

Patients with Cirrhosis

Eight stable ambulant male patients with biopsy-proven cirrhosis (5 alcoholic and 3 chronic hepatitis B) of the liver participated in the study. Their clinical and biochemical characteristics are listed in Table 1. Three of them had been taking lactitol for the management of portosystemic encephalopathy

Table 1. Clinical and biochemical details of patients with cirrhosis

	Weight (kg)	Creatinine Clearance ($ml \cdot min^{-1}$)	Albumin ($g \cdot l^{-1}$)	Bili-rubin ($mmol \cdot 1^{-1}$)	Bile acids ($mmol \cdot l^{-1}$)	GOT (U·l−1)	ABT[a] (%dose·kg·mmol−1 CO2)	GEC[b] ($mg \cdot min^{-1}$)	ICG[c] (min^{-1})
Median	79	71	30	33	32	31	0.20	316	0.064
Range	(64-105)	(27-138)	(18-33)	(7-64)	(1-46)	(16-99)	(0.09-0.48)	(250-350)	(0.043-0.139)
Normal values by the methods utilized			>32	<26	<6	<20	>0.6	>370	>0.120

[a] ABT: Aminopyrine breath test, normal 0.6-1.0 %dose × kg·mmol^{-1} CO_2; [b] GEC: Galactose elimination capacity, normal 370-640 mg·min^{-1}; [c] ICG: Fractional rate of disappearance of indocyanine green, normal 0.12-0.28 min^{-1}

for 9 to 70 months. The remaining patients did not require treatment for hepatic encephalpathy.

All subjects gave their informed consent to participation in the study.

Protocol

The subjects were admitted to the Clinical Pharmacology Unit on the morning of the study, after an overnight fast, and an indwelling catheter was placed in an antecubital vein. After obtaining baseline blood and urine samples, the patients ingested lactitol 0.5 g/kg body weight dissolved in 300 ml lukewarm water. No additional intake of fluids or food was permitted for the subsequent 4 h. 10 ml blood samples were obtained 5, 10, 30, 60, 120 and 240 min after ingesting the lactitol. Urine samples were obtained after 1 h, 2 h and 4 h, and then in fractions from 4 to 12 h and 12 to 24 h. To obtain the urine samples the patients were asked to empty the bladder. The patients were under the supervision of the nursing staff for 4 h.

Aliquots of blood 1 ml were immediately added to 2 ml 0.66 N perchloric acid. Following centrifugation, the supernatant was kept at −20 °C for the subsequent determination of D- and L-lactate. The concentration of glucose was measured in plasma. Serum was obtained and frozen at −20 °C for the assay of lactitol.

The volume and pH of the voided urine samples were measured immediately, and aliquots were frozen at −20 °C for the subsequent determination of lactitol.

Analytical Methods

Lactitol in serum and urine was assayed by HPLC with a Dionex (Dionex Corp, Sunnyvale, CA, USA) pulsed amperometric detector [8]. Raffinose (Merck, Darmstadt, FRG) was used as the internal standard. Serum and urine samples 1.0 ml were mixed with an equal volume of acetonitrile. The HPLC system (Waters Assoc., Milford, MA, USA) operated with a 250 × 4.6 mm stainless steel column packed with Supelcosil NH_2 5 μm and was fitted with a Supelcosil NH_2 guard column (Supelco, Gland, Switzerland). The mobile phase consisted of water : acetonitrile 25 : 75 (v : v), and the post-column reagent was 0.2M NaOH. The flow rate was set at 1.2 ml·min^{-1}.

Table 2. Blood lactate and plasma glucose, following the administration of lactitol ($mmol \cdot l^{-1}$; median and range in brackets)

	Cirrhotic patients	Healthy subjects
Glucose	Baseline	5.80 (5.3-18.9)	4.40 (4.1-5.0)
	Maximal increment following lactitol	0.25 (0 -1.4)	0.15 (0 -0.6)
L-lactate	Baseline	1.32 (0.76-1.66)	1.11 (0.76-1.16)
	Maximal increment following lactitol	0.08 (0 -0.20)	0.04 (0 -0.14)
D-lactate	Baseline	0.18 (0.12-0.21)	0.32 (0.26-0.39)
	Maximal increment following lactitol	0.04 (0.01-0.13)	0 (0 -0.05)

The detection limits were 10 μg·ml^{-1} in serum and 50 μg·ml^{-1} in urine at a signal to noise ratio of 2 : 1. Linear calibration curves were obtained from the plot of the ratio of the peak height of lactitol to raffinose versus concentration between 0-100 μg·ml^{-1} and 0-200 μg·ml^{-1} for serum and urine, respectively. The coefficients of variation were 11% at 50 μg·ml^{-1} ($n = 10$) and 14% at 100 μg·ml^{-1} ($n = 10$) for serum and urine, respectively.

D- and L-lactate were assayed by stereospecific enzymatic reactions. The L-lactate analysis used a kit from Boehringer (Cham, Switzerland). For the determination of D-lactate the suspension of the L-LDH enzyme was replaced by the D-LDH enzyme (Boehringer, Cham, Switzerland). The limit of detection of both D and L lactate was 0.08 mmol·l^{-1}. Standard curves were linear up to the concentration of 5.56 mmol·l^{-1}, and the coefficient of variation

was 1.5%. Glucose was assayed enzymatically (Glucoquant, Boehringer, Switzerland) with an automatic Cobas-Bio analytical system (Hoffmann-La Roche, Basel, Switzerland).

Results and Discussion

All subjects tolerated the compound well, although they all experienced abdominal bloating, increased flatulence and minor abdominal cramping following such a large dose of lactitol.

In all subjects the serum concentration of lactitol was below the limit of detection ($10\ \mu g \cdot ml^{-1}$) for the duration of the study. Assuming distribution of absorbed lactitol in the extracellular space, only 0.5% of the administered dose would have to be in the extracellular compartment to yield a plasma concentration exceeding $10\ \mu g \cdot ml^{-1}$. Thus, the observation that lactitol could not be detected in blood following the administration of an oral dose exceeding 30 g active substance indicates that the absorption of lactitol was negligible in normal subjects as well as in patients with cirrhosis and portal hypertension.

This was confirmed by the minimal urinary excretion of the unmetabolized compound, which was less than 500 mg over 24 h. The cirrhotic patients excreted an average of 177 ± 142 mg (mean $\pm$ SD) in 24 h, corresponding to $0.46 \pm 0.43\%$ of the administered dose. The healthy volunteers excreted 117 ± 50 mg, corresponding to $0.35 \pm 0.14\%$ of the dose. In none of the subject did the excreted amount of lactitol exceed 1.5% of the administered dose. There was no difference between the three patients who had been taking lactitol on a regular basis and the other patients, which means that prolonged consumption of the compound had not altered its absorption. The low gastrointestinal absorption found here is consistent with the results of jejunal perfusion studies in normal volunteers, which did not show any absorption of the disaccharide from the small intestine [10].

Lactitol is rapidly metabolized by the bacterial flora of the colon and D- and L-lactate are two of the many metabolites found. Lactate might be absorbed and could interfere with acid-base homeostasis. However, no increase in blood D- or L-lactate was seen over 4 h after administration of lactitol (Table 2).

In addition to lactate, glucose might be a clinically relevant metabolite of lactitol resulting from the enzymatic conversion of galactose, which is a constituent of lactitol, to glucose. As shown in Table 2, however, lactitol did not lead to an increase in plasma glucose, even in the two patients who were diabetic. Similarly, no glycosuria was detected following the administration of lactitol compared to pretreatment values.

It is concluded that lactitol is absorbed to a minimal extent from the gastrointestinal tract in healthy volunteers and patients with cirrhosis, and that metabolism of the compound by intestinal bacteria does not interfere with glucose and lactate homeostasis.

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Bernhard H. Lauterburg
Department of Clinical Pharmacology
Murtenstraße 35
CH-3010 Bern, Switzerland