Eur J Clin Pharmacol (1989) 37: 205-207

European Journal of Clinical Pharmacology

Effect of one month of lactitol treatment on calcium metabolism in man

B. Egger[1], V. Arnera[2], J.-B. Llull[2], and B. H. Lauterburg[1]

[1] Department of Clinical Pharmacology, University of Berne, Berne and [2] Zyma SA, Nyon, Switzerland

Summary. The chronic use of lactitol as a food additive or laxative might adversely affect calcium homeostasis. Its effect on calcium metabolism has been examined in an open cross-over study in 12 volunteers given 20-40 g lactitol per day for one month.

Compared to a control period without lactitol, the disaccharide did not alter the urinary excretion of calcium, inorganic phosphate or hydroxyproline, nor did it alter the circulating levels of calcium, phosphate, alkaline phosphatase, parathormone and osteocalcin.

Chronic treatment with lactitol in laxative doses had no measurable effect on calcium metabolism in man.

Key words: lactitol; calcium homeostasis, osteocalcin, parathormone, healthy volunteers

Lactitol (beta-galactosido-sorbitol), initially developed as a food additive [1], is as effective as lactulose in the treatment of patients with hepatic encephalopathy [2, 3] and constipation. Lactitol is neither absorbed nor metabolized in the small intestine, and passes unchanged into the large bowel, where it is metabolized by bacteria into organic acids and CO_2 [4].

Lactitol might interfere with calcium homeostasis if taken for a prolonged period as a laxative or food additive [5-8]. In rats, lactitol has been shown to increase the intestinal absorption of calcium and its body retention [9]. In contrast, lactitol acutely decreases the fractional absorption of calcium in man [10]. Calcium absorption is also decreased in lactase-deficient subjects ingesting lactose [11], which, from a pathophysiological point of view, may be considered to be similar to subjects taking lactitol. A decrease in the absorption of calcium for an extended period of time could adversely affect bone structure. Therefore, the effect of long-term, low dose treatment with lactitol on calcium metabolism was investigated in non-constipated and constipated healthy volunteers maintained on their usual diets and pursuing their regular daily activities.

Subjects and methods

A randomized, open, cross-over study of calcium metabolism was performed during one month of lactitol treatment and one month without lactitol. The study was approved by the institutional Ethics Committee.

Subjects

Twelve healthy volunteers (6 females, 6 males), ranging in age from 20 to 43 years (mean 31 years) gave written informed consent to participate in the study. All subjects were free from any known disease affecting calcium metabolism or gut function according to the results of an interview, physical examination and normal laboratory tests. With the exception of three women on contraceptive steroids, none of the subjects had taken any medication (especially no antacid, calcium, laxative or vitamin D products) within the 3 months preceding the trial. Five of the twelve participants complained of constipation. The individuals were divided into two groups (A and B) according to a randomization list.

Experimental procedures

Group A (3 females, 3 males) started on lactitol (Zy 15060; Zyma SA, Nyon) treatment 20 g as a single evening dose with 200 ml water during the first month (Days 1-28) followed by no treatment (constipated volunteers were allowed to take Dr. Kousa Wheat

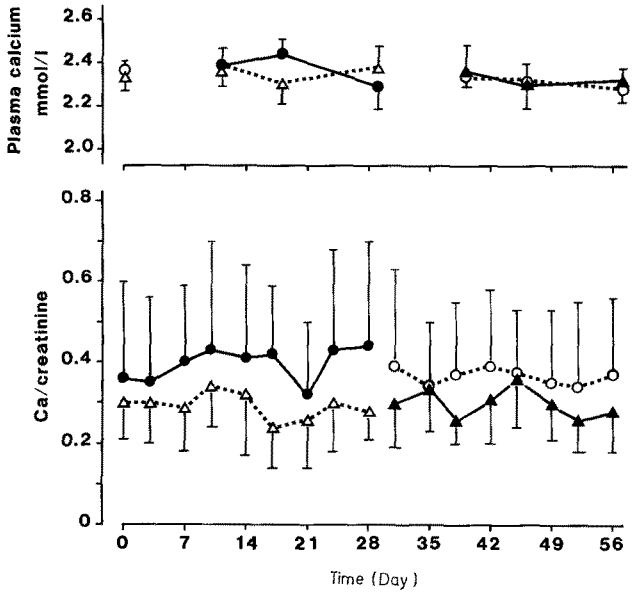

Fig. 1. Plasma concentration of calcium and calcium to creatinine ratio in 24-h urine from Group A who received lactitol *(closed circles)* followed by no treatment *(open circles)*, and in Group B who received no treatment *(open triangles)* followed by lactitol *(closed triangles)*. 6 subjects in each group, mean (SD)

Bran) during the second month (Days 29–56). Group B (3 females, 3 males) started with no treatment followed by lactitol.

Phosphate and alkaline phosphatase in plasma, and parathormone and osteocalcin in serum were measured twice (Days 29 and 57); plasma calcium on Days 11, 18, 29, 39, 46 and 57; 24-h urinary inorganic phosphate on Days 28 and 56; 24-h urinary calcium and creatinine were measured twice weekly. Calcium and hydroxyproline were determined in 2 h spot urine samples, collected from 07.00 to 09.00 h, (preceded by a calcium and collagen-free meal the evening before) on Days 9, 23, 37 and 51.

Laboratory investigations

All laboratory investigations were carried out in the Central Chemical Laboratories of the University Hospital of Berne (standard Greiner autoanalyzer: G400), except for parathormone, which was measured by RIA in the experimental laboratory for calcium metabolism (Orthopedic Department Balgrist, University of Zürich) and osteocalcin, measured (ORIS-Kit, France) in the Central Chemical Laboratories of the University of Geneva.

Statistical analysis

Data were analyzed by two way analysis of variance.

Results and discussion

All participants completed the study. Monitoring visits were scheduled at each blood sampling time. Every volunteer complained of slight meteorism and flatulence during the first days of lactitol treatment. Lactitol, used as a laxative at the dose of 20 g/day, was effective in 3 out of 5 constipated persons, and two others had to increase the dose to 30 g/day and 40 g/day, respectively, to have regular daily bowel movements. No problems were observed during the drug-free and bran treatment periods. Although no compliance marker was used, the fact that all 24-h and 2-h urines were collected on time and that the excreted creatinine was remarkably constant throughout the study speaks for the reliability of the subjects.

The effect of lactitol on bone metabolism was assessed by measuring parathormone, osteocalcin – a clinically useful marker of bone formation [12–14], and alkaline phosphatase, another product of osteoblasts. As shown in Table 1, none of these three markers nor inorganic phosphate in plasma or the phosphate to creatinine ratio in urine changed during lactitol treatment compared to the control period and pretreatment values. Similarly, the early morning urinary excretion of hydroxyproline and calcium remained stable (Table 1); hydroxyproline is a sensitive index of (bony) collagen metabolism [15], and fasting urinary calcium mirrors net bone resorption. The plasma calcium level did not change (Fig. 1). In spite of the many factors affecting the urinary excretion of calcium, the calcium to creatinine ratio was remarkably constant during the study (Fig. 1). The statistically significant difference between the two

Table 1. Effect of one month of lactitol treatment on indices of calcium homeostasis

Parameters	Pretreatment	Control-month	Lactitol-month
Parathormone (pgeq hPTH/ml)	438 (154)[a]	462 (165)	462 (162)
Osteocalcin (μg/l)	13.9 (3.53)	10.6 (2.53)	12.03 (3.33)
Alkaline phosphatase (U/l)	53.4 (16.9)	46.8 (13.5)	48.6 (12.9)
Plasma phosphate (mmol/l)	1.98 (0.35)	2.24 (0.52)	2.51 (0.72)
Urine phosphate[b]	1.01 (0.20)	1.05 (0.15)	0.99 (0.16)
Calcium excretion in 2 h (mmol)[c]	–	0.31 (0.24)	0.32 (0.39)
Hydroxyproline excretion in 2 h (mmol)[c]	–	25 (11)	22 (10)

[a] Mean (SD), $n = 12$; [b] urine phosphate/urine creatinine; [c] excreted in 2 h following a calcium- and collagen-free evening meal and an overnight fast

treatment groups suggested by analysis of variance was not confirmed by Student's *t*-test.

In the present study lactitol did not have any measurable effect on the urinary excretion of calcium or on established markers of calcium metabolism. Since considerable day to day and interindividual variation in many markers of calcium metabolism is observed, the effect of a drug could easily be missed if single samples are compared. The cross-over design of the present study and the repeat sampling to assess the parameters subject to substantial day to day variation minimized the risk of missing a biologically significant effect of the drug on calcium homeostasis. The present data indicate that the long-term administration of lactitol, used as a laxative in low dosage of 20–40 g daily, does not interfere with calcium absorption from the gastrointestinal tract, the turnover of calcium in bone, or the handling of calcium by the kidneys. It may safely be used for prolonged periods of time.

References

1. Van Velthuijsen JA (1979) Food additives derived from lactose; lactitol and lactitol palmitate. J Agric Food Chem 27: 680–686
2. Lanthier PL, Morgan MY (1985) Lactitol in the treatment of chronic hepatic encephalopathy: An open comparison with lactulose. Gut 26: 415–420
3. Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L, Gil S, Garcia-Ramos G (1987) Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: A double-blind, randomized clinical trial. Hepatology 7: 639–643
4. Patil DH, Westaby D, Mahida YR, Palmer KR, Rees R, Clark ML, Dawson AM, Silk DBA (1978) Comparative modes of action of lactitol and lactulose in the treatment of hepatic encephalopathy. Gut 28: 255–259
5. Dragstedt LR, Peacock SC (1923) Studies on the pathogenesis of tetany. The control of parathyroid tetany by diet. Am J Physiol 64: 424–434
6. Fournier P, Depuis Y (1960) Pouvoir antirachitique de composés divers, dits de structure: Lactose, glucosamine, L-xylose, mannitol. CR Acad Sci Paris 250: 3050–3052
7. Fournier P, Gambier J, Fontaine N (1967) Effets d'une ingestion prolongée de sorbitol sur l'utilisation du calcium et sur l'ossification du rat. CR Acad Sci Paris 264: 1301–1304
8. Lengemann JW, Wassermann RH, Comar CL (1959) Studies on the enhancement of radio Ca and radio Sr absorption by lactose in the rat. J Nutr 68: 443–445
9. Amman P, Rizzoli R, Fleisch H (1988) Influence of the disaccharide lactitol on intestinal absorption and body retention of calcium in rats. J Nutr 118: 793–795
10. Griessen M, Speich PV, Infante F, Bartholdi P, Cochet B, Donath A, Courvoisier B, Bonjour JP (1989) Effect of absorbable and non-absorbable sugars on intestinal calcium absorption in humans. Gastroenterology 96: 769–775
11. Cochet B, Jung A, Griessen M, Bartholdi P, Schaller P, Donath A (1983) Effects of lactose on intestinal calcium absorption in normal and lactase-deficient subjects. Gastroenterology 84: 935–940
12. Price PA, Parthemore JG, Deftos LJ (1980) New biochemical marker for bone metabolism. J Clin Invest 66: 878–883
13. Gundberg CM, Lian JB, Gallop PM, Steinberg JJ (1983) Urinary gamma-carboxy-glutamic acid and serum osteocalcin as bone markers: Studies in osteoporosis and Paget's disease. J Clin Endocrinol Metab 57: 1221–1225
14. Slovik DM, Gundberg CM, Neer RM, Lian JB (1984) Clinical evaluation of bone turnover by serum osteocalcin measurements in a hospital setting. J Clin Endocrinol Metab 59: 228–230
15. Krane SM, Krantowita FG, Byrne M, Pinnell SR, Singer F (1977) Urinary excretion of hydroxylysine and its glycosides as an index of collagen degradation. J Clin Invest 59: 819–827

Received: February 8, 1989
accepted: March 4, 1989

Bernhard H. Lauterburg, M.D.
Department of Clinical Pharmacology
University of Berne
Murtenstrasse 35
CH-3010 Berne, Switzerland