β-Galactosidase Tablets in the Treatment of Lactose Intolerance in Pediatrics

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• **Lactose-intolerant children manifest diminished or nonexistent intestinal lactase activity, resulting in flatulence, abdominal pain, and diarrhea. To assess the hydrolytic capability of lactase-containing tablets taken immediately before oral lactose challenge, we studied 18 children previously identified as being lactose intolerant and having no underlying organic gastrointestinal disease. Subjects had a mean (± SEM) age of 11.4 ± 3.4 years; 72% were male. At time of the study, lactase-containing tablets or placebo tablets were ingested (double-blind) immediately before drinking a solution of lactose. Breath samples were obtained for hydrogen analysis at 30-minute intervals during a 2-hour period, and clinical symptoms were monitored. In lactose-intolerant patients, hydrogen production was significantly greater following placebo (maximum hydrogen excretion, approximately 60 ppm) compared with lactase-containing tablets (maximum hydrogen excretion, 7 ppm). Increased hydrogen production was associated with clinical symptoms including abdominal pain (89% of subjects following placebo ingestion), bloating (83%), diarrhea (61%), and flatulence (44%). These results indicate, therefore, that coingestion of lactose and lactase-containing tablets significantly reduces both breath hydrogen excretion and clinical symptoms associated with lactose intolerance.**

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Lactose intolerance, a consequence of decreased or absent intestinal β-galactosidase (lactase) activity, is a common finding in the pediatric population.[1,2] Symptoms related to lactose intolerance are often transient, presenting as a result of mucosal injury associated with either bacterial or viral enteritis.[3,4] Other clinical states characterized by intestinal brush-border injury or altered bowel flora (eg, gluten-sensitive enteropathy and gastrointestinal surgery) may be complicated by secondary lactase deficiency.[5,6] A rare, congenital form of this disorder characteristically presents within the first few days of life, following introduction of lactose in breast milk or formula.[7,8] In otherwise healthy older children and adults, the inability to hydrolyze lactose to its component sugars, glucose and galactose, is commonly referred to as "late-onset" or "acquired" lactase deficiency. This type of enzyme disorder is thought to occur as a heritable, autosomal recessive trait, exhibiting a wide variation in incidence among different ethnic groups. Symptoms, while usually noted after 3 to 5 years of age, may occur as late as adolescence.[1,2]

The clinical consequences of lactase deficiency result from the bacterial hydrolysis of lactose in the cecum and colon, resulting in production of hydrogen, carbon dioxide, and short-chain organic acids.[9-11] Increased evolution of gas, and the osmotic load presented to the colon secondary to bacterial fermentation can lead to multiple symptoms, including abdominal pain, distention, flatus, eructation, and watery, often acidic stools. In children with lactase deficiency, these symptoms may result in anorexia and weight loss.

Because milk and dairy products are important sources of both macronutrients and micronutrients in the pediatric diet, a convenient treatment for lactose intolerance may obviate the need for specialized nutritional management. Current available therapies include commercially available predigested milk and dairy products as well as fungal or yeast-derived β-galactosidases added to lactose-containing liquids. While this latter treatment is effective, 12 to 24 hours is required for adequate (ie, >60%) in vitro lactose hydrolysis. Recent studies have described the utility of adding β-galactosidases to milk immediately before ingestion by adults[12,13] and children[14,15] in decreasing both the production of breath hydrogen and the clinical symptoms associated with lactose intolerance. To determine an effective treatment alternative for children with

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symptomatic lactose intolerance, we evaluated the efficacy of a tablet form of β-galactosidase taken immediately before an oral lactose challenge.

PATIENTS AND METHODS

Patient Selection

Patients were selected from among those referred to the Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla. Patients presenting with chronic nonspecific abdominal pain, with or without diarrhea, were evaluated for the presence of late-onset primary lactose intolerance.

Children with underlying gastrointestinal disease (eg, inflammatory bowel disease, acute gastroenteritis, and celiac disease) or manifestations of acute/chronic malnutrition or growth failure[16] were excluded from the study. Routine patient screening included a physical examination; determinations of complete blood cell count with differential cell count, platelet count, erythrocyte sedimentation rate, and liver function; and urinalysis and urine culture. Those with normal results of screening studies subsequently underwent breath hydrogen analysis, as described below.

From December 1, 1987, through November 30, 1988, a total of 18 patients with late-onset lactose intolerance were enrolled in the study. The protocol was approved by The Committee for the Protection of Human Subjects (Institutional Review Board), New York Medical College.

Hydrogen Breath Testing

All patients fasted for a minimum of 8 hours before the hydrogen breath test was performed and had not received antibiotics for at least 2 weeks before the test. Participants were placed on a gluten- and lactose-free diet for 24 hours before testing to minimize basal hydrogen production. Each patient received lactose (2 g/kg of body weight up to a maximum of 50 g) and had serial breath samples (0, 30, 60, 90, and 120 minutes following lactose ingestion) tested for the presence of hydrogen. Patients who did not produce hydrogen after a carbohydrate challenge, or those who exhibited baseline (zero time) breath hydrogen levels greater than 10 ppm, were excluded from the study.

Lactose-intolerant patients who agreed to participate underwent two additional breath tests at least 2 weeks apart, during which either lactase-containing tablets or placebo tablets were administered in a double-blind, cross-over fashion. The investigator initially determined which tablet to administer in a randomized fashion by lot. Tablets containing lactase (β-galactosidase produced from *Aspergillus oryzae*) and placebo of inert excipient were supplied by Lactaid Inc, Pleasantville, NJ. Each active tablet contained 3000 (Food Chemical Codex Units) of β-galactosidase (optimum pH, approximately 4.5). Participants chewed and swallowed one tablet per 5 g of lactose immediately before carbohydrate challenge. There were no sensory differences (ie, taste or texture) between the active and placebo tablets.

End expiratory breath samples were collected in a gas-tight syringe and analyzed for hydrogen concentration following separation with use of a gas chromatograph (Carle Model AGC 111, Hache Inc, Loveland, Colo) with a 275-cm, 5 Å molecular sieve column (45/50 mesh) equipped with a thermal conductivity detector. The system was standardized before each use with a reference gas consisting of 100 ppm of hydrogen in nitrogen (MG Scientific Gases, Northbranch, NJ). Hydrogen concentration was quantitated with use of a computing integrator (Shimadzu CR3A, Shimadzu Inc, Columbia, Md). Breath hydrogen levels 10 ppm above baseline were considered positive for lactose malabsorption.[15]

Symptom Evaluation

During each of the carbohydrate challenges, patients were interviewed about the presence or absence of abdominal pain, gas, bloating, diarrhea, or flatulence. In addition, patients recorded their symptoms on a questionnaire, which was evaluated for severity of symptoms (on a scale of 1 to 5, with 1 being absence of symptoms and 5 being severe symptoms) independent of breath analysis results.

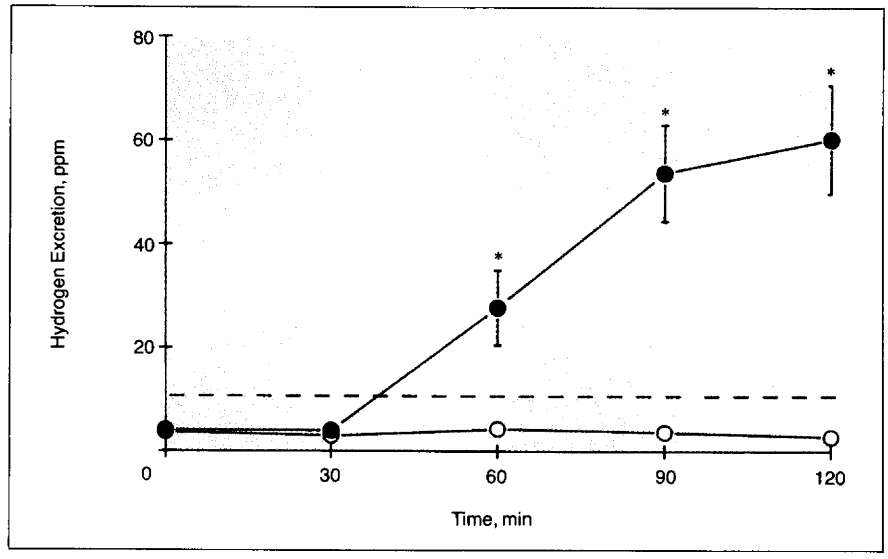
Statistical Analysis

Comparisons between lactose-tolerant and lactose-intolerant patients were made with use of both χ^2 analysis and Student's t test for unpaired samples (two-tailed). Differences in hydrogen excretion associated with placebo and lactase treatment were assessed with use of Student's t test for paired data (two-tailed).[17]

RESULTS

During the examination of 160 children (mean ± SEM age, 9.3 ± 0.4 years) referred because of chronic recurrent abdominal pain, 55 (34%) were identified as being lactose intolerant. Patients were classified as being either lactose-tolerant (normal) or lactose-intolerant based on the results of breath hydrogen analysis every 30 minutes for a total of 120 minutes. In lactose-tolerant children (Fig 1), breath hydrogen excretion did not exceed 10 ppm, as shown by the broken line in Fig 1, and averaged (mean ± SEM) 2.3 + 0.2 ppm up to 120 minutes. Breath hydrogen quantitation of lactose-intolerant children exceeded 10 ppm by 60 minutes and remained significantly elevated ($P<.01$, normal

Fig 1.—Time course of breath hydrogen excretion in lactose-tolerant (open circles) and lactose-intolerant (closed circles) patients (N = 160). Data shown are the mean (± SEM) breath hydrogen excretion values; where not depicted, SEM is within the data point. The dashed line represents a breath hydrogen level of 10 ppm; breath hydrogen concentration above 10 ppm is diagnostic of lactose malabsorption. Asterisk indicates $P<.01$, normal vs control.



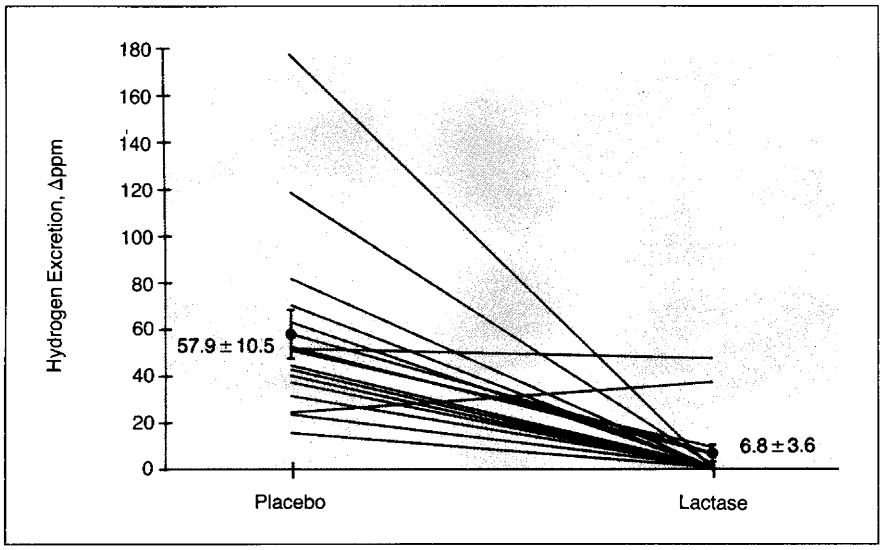


Fig 2.—Breath hydrogen excretion of 18 patients determined 120 minutes after lactose ingestion with either placebo- or lactase-containing tablets. Data shown are individual values of net (total minus basal) breath hydrogen excretion. Solid circles indicate the mean (±SEM) values ($P<.01$, placebo vs lactase tablets).

Symptoms Recorded by 18 Study Patients*

Symptom	No. of Patients: Lactase Group	No. of Patients: Placebo Group
Diarrhea	1	11
Bloating	...	15
Abdominal pain	1	16
Flatulence	...	8
Total	**2**	**50**

*Symptoms were recorded following lactose challenge (2 g/kg; maximum dose, 50 g) plus either placebo or lactase tablets (1 tablet per 5 g of lactose) (see "Patients and Methods" section).

vs lactose-intolerant; N = 160) for the duration of the test period. There were no differences at zero time (3.7 ± 0.44 vs 4.1 ± 1.43 ppm) or at 30 minutes (2.9 ± 0.36 vs 3.9 ± 1.28 ppm) (mean ± SEM), comparing breath hydrogen levels for all normal and lactose-intolerant patients, respectively.

Eighteen of the 55 patients identified as lactose intolerant agreed to participate in this study. The demographics of the participants were not different from those of the nonparticipants. The mean age of the participants was 11.4 ± 3.4 years, which was not significantly different from that of the 160 children initially screened for lactose intolerance. The sex distribution was 72% male compared with 47.5% of the initial group. Figure 2 shows that placebo administration, followed by lactose challenge, resulted in a mean (±SEM) net breath hydrogen value of 57.9 ± 10.5 ppm at 120 minutes (net hydrogen excretion equals total minus basal [zero time] levels). In contrast, lactose-intolerant patients produced only 6.8 ± 3.6 ppm of hydrogen at 120 minutes ($P<.01$, n = 18). Figure 2 also shows maximum net breath hydrogen values for each patient following both placebo and lactase administration. In 16 (89%) of the 18 participants, lactase pretreatment successfully lowered maximal (120-minute) net breath hydrogen levels to below the 10-ppm threshold for malabsorption ($P<.001$).

The Table lists the clinical symptoms associated with lactose challenge in this pediatric population. Following placebo, 89% of patients experienced abdominal pain, 83% experienced bloating, 61% experienced diarrhea, and 44% experienced flatulence. In two (11%) of the 18 patients, symptoms were reported despite pretreatment with lactase calculated to hydrolyze the ingested lactose load.

COMMENT

Lactose malabsorption resulting from lactase deficiency can be detected by a lack of rise in plasma glucose level following ingestion of lactose. A less invasive, more accurate method for the detection of lactase deficiency is the measurement of breath hydrogen. Because hydrogen is not produced as a result of normal metabolism in humans, bacterial fermentation of nonhydrolyzed lactose produces hydrogen that diffuses into the blood and can be measured in expired breath. The presence of increasing amounts of breath hydrogen with time following an oral lactose load suggests lactase deficiency. In some 20% of patients studied, however, colonic bacteria were incapable of producing hydrogen when presented with a nonmetabolizable carbohydrate, lactulose.[18] In these individuals, determination of breath hydrogen excretion is of little diagnostic value. Our study, therefore, included patients who were symptomatic and capable of producing hydrogen gas.

Numerous clinical studies have described the efficacy of the predigestion of lactose in the elimination of symptoms associated with lactase deficiency.[12-15] These investigations included the predigestion of milk or lactose-containing formula before ingestion. However, there has been no correlation of symptoms with breath hydrogen production in older children and adolescents, nor an evaluation of the effectiveness of lactase and lactose co-administration. We evaluated the effectiveness of lactase-containing tablets in the reduction of breath hydrogen excretion and clinical symptoms commonly associated with lactase deficiency. The participants were healthy, well-nourished children diagnosed as being lactose intolerant. Breath hydrogen was measured every 30 minutes for 2 hours following lactose ingestion, rather than for 3 or 6 hours as suggested by some investigators,[19,20] as breath hydrogen excretion was significantly greater than the basal level by 60 minutes. Our results show that coingestion of lactose and lactase-containing tablets significantly reduced breath hydrogen excretion in 16 (89%) or 18 patients. This reduction in hydrogen excretion was temporally associated with a decrease of reported symptoms in this group of lactose-intolerant patients. Use of a convenient, palatable tablet form of lactase offers obvious advantages, allowing for the potential liberal-

ization of dietary lactose intake. The inability of lactase tablets to lower breath hydrogen excretion and ameliorate symptoms in two patients may have been secondary to several factors. For example, gastric hyperacidity may have resulted in decreased activity of the enzyme (optimum pH, approximately 4.5). Alternatively, selected patients may be exquisitely sensitive to small amounts of unhydrolyzed carbohydrate, requiring increased exogenous lactase.

Lactose intolerance in this study was evaluated using a standard carbohydrate challenge, which employs a nonbuffered solution of lactose in water (pH 6.2). It is likely that the pH of this solution in the stomach approximated the optimum of the exogenous lactase and resulted in relatively rapid hydrolysis of the ingested lactose. Caution must be exercised, however, when extrapolating from results obtained with use of a lactose solution to results achieved with ingestion of lactose-containing foods. Hydrolysis of a lactose solution is not limited by factors such as degree of mastication, mechanical disruption, enzymatic predigestion of complex carbohydrates, and effective exposure of lactose to the exogenous enzyme. Furthermore, the buffering effect of dietary proteins and the variability in gastric emptying time as a consequence of dietary composition may influence the effectiveness of exogenous lactase. Further studies with various lactose-containing foods are therefore required to establish the utility of oral lactase administration in the reduction of both breath hydrogen excretion and related gastrointestinal symptoms associated with lactose intolerance in children.

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