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A COMPARISON OF SYMPTOMS AFTER THE CONSUMPTION OF MILK OR LACTOSE-HYDROLYZED MILK BY PEOPLE WITH SELF-REPORTED SEVERE LACTOSE INTOLERANCE

FABRIZIO L. SUAREZ, M.D., DENNIS A. SAVAIANO, PH.D., AND MICHAEL D. LEVITT, M.D.

Abstract Background. Ingestion of a large dose of the milk sugar lactose — for example, the 50-g load in 1 liter of milk — causes symptoms such as abdominal pain, diarrhea, bloating, and flatulence in the majority of people with lactose malabsorption. It is uncertain whether the ingestion of more common doses of lactose, such as the amount in 240 ml (8 oz) of milk, causes symptoms. Some people insist that even smaller quantities of milk, such as the amount used with cereal or coffee, cause severe gastrointestinal distress.

Methods. In a randomized, double-blind, crossover trial, we evaluated gastrointestinal symptoms in 30 people (mean age, 29.4 years; range, 18 to 50) who reported severe lactose intolerance and said they consistently had symptoms after ingesting less than 240 ml of milk. The ability to digest lactose was assessed by measuring the subjects' end-alveolar hydrogen concentration after they ingested 15 g of lactose in 250 ml of water. Subjects then received either 240 ml of lactose-hydrolyzed milk containing 2 percent fat or 240 ml of milk containing 2 percent fat and sweetened with aspartame to approximate the taste of lactose-hydrolyzed milk; each type of milk was administered daily with breakfast for a one-week period. Using a standardized scale, subjects

rated the occurrence and severity of bloating, abdominal pain, diarrhea, and flatus and recorded each passage of flatus.

Results. Twenty-one participants were classified as having lactose malabsorption and nine as being able to absorb lactose. During the study periods, gastrointestinal symptoms were minimal (mean symptom-severity scores for bloating, abdominal pain, diarrhea, and flatus between 0.1 and 1.2 [1 indicated trivial symptoms; and 2, mild symptoms]). When the periods were compared, there were no statistically significant differences in the severity of these four gastrointestinal symptoms. For the lactose-malabsorption group, the mean (\pm SEM) difference in episodes of flatus per day was 2.5 ± 1.1 (95 percent confidence interval, 0.2 to 4.8). Daily dietary records indicated a high degree of compliance, with no additional sources of lactose reported.

Conclusions. People who identify themselves as severely lactose-intolerant may mistakenly attribute a variety of abdominal symptoms to lactose intolerance. When lactose intake is limited to the equivalent of 240 ml of milk or less a day, symptoms are likely to be negligible and the use of lactose-digestive aids unnecessary. (N Engl J Med 1995;333:1-4.)

THE milk sugar lactose must be hydrolyzed by a lactase at the intestinal brush border before it can be absorbed. After weaning, there is a genetically programmed reduction in lactase activity in many people that cannot be altered by the ingestion of milk.¹⁻³ Such people acquire what has been variously termed “primary acquired lactase deficiency,” “lactase nonpersistence” or “lactose malabsorption.” The ability to maintain throughout adult life the levels of lactase characteristic of infancy is inherited through a single, highly penetrant autosomal dominant gene^{4,5} located on chromosome 2.⁶ People of northern European descent generally have high lactase levels throughout adulthood. Most other people become lactase-nonper-

sistent.^{5,7} About 25 percent of adults in the United States and 75 percent worldwide have lactose malabsorption.^{7,8}

Ingestion of a large dose of lactose, such as the 50-g load in 1 liter (1.06 qt) of milk, causes diarrhea, bloating, and flatulence in the majority of people with lactose malabsorption.⁹ There is controversy, however, about such people's tolerance of smaller doses of lactose, such as the amount found in 240 ml (8 oz) of milk. One uncontrolled study suggested that the majority of people with lactose malabsorption have appreciable symptoms after drinking 240 ml of milk.¹⁰ In contrast, a blinded study suggested that most of those with malabsorption tolerate 240 ml of milk without recognizable symptoms.⁸ Nevertheless, it is extremely common for patients to insist that ingesting very small quantities of milk, such as the amount used with cereal or coffee, causes severe gastrointestinal distress. This concept of severe intolerance has been nurtured by innumerable articles in the news media and advertisements for lactose-digestive aids. People who believe that they are

From the Department of Food Science and Nutrition, University of Minnesota, St. Paul (F.L.S., D.A.S.), and the Minneapolis Veterans Affairs Medical Center, Minneapolis (M.D.L.). Address reprint requests to Dr. Levitt at the Minneapolis Veterans Affairs Medical Center, 1 Veterans Dr., Minneapolis, MN 55417.

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severely lactose-intolerant have not been adequately represented in previous trials, which have evaluated people with lactose malabsorption independently of whether or not they considered themselves lactose-intolerant.¹¹⁻¹⁴

In a self-selected group of people with severe lactose intolerance, we evaluated gastrointestinal symptoms after they drank 240 ml of milk daily for one-week periods. Our findings suggest that a variety of abdominal complaints are frequently misattributed to lactose intolerance.

METHODS

Subjects

People who believed they were severely lactose-intolerant were recruited through advertisements posted at the Minneapolis Veterans Affairs Medical Center and the University of Minnesota campus. Seventy-eight initial respondents were screened through a telephone questionnaire. Subjects were excluded if they did not report consistently having symptoms (abdominal pain, bloating, flatulence, or diarrhea) after drinking less than 240 ml of milk; if they had undergone gastrointestinal surgery, had other major illnesses, or received antibiotic therapy within the previous two months; or if they indicated that they could not consume aspartame. Of the 30 people selected for further study, 10 avoided milk in any form and 20 consistently used a commercial lactose-digestive aid (lactose-hydrolyzed milk or a lactase preparation).

Lactose Absorption

The ability of the 30 subjects to digest lactose was determined by measuring their end-alveolar hydrogen concentrations hourly for five hours after they ingested 15 g of lactose in 250 ml of water (0.18 mol per liter). Subjects were classified as having lactose malabsorption if their breath hydrogen concentrations increased by more than 10 parts per million (ppm) (0.9×10^{-6} g of hydrogen per liter of air or $0.45 \mu\text{mol}$ per liter).¹⁵ The ability of the colonic flora to produce hydrogen through fermentation in response to carbohydrate malabsorption was tested in seven of the nine subjects who were able to absorb lactose after they ingested 10 g of lactulose (Xactdose, South Beloit, Ill.) in 250 ml of water (0.12 mol per liter). Lactulose is a nonabsorbable disaccharide that is fermented by the same enzymatic pathway as lactose.

The protocol was approved by the Human Subjects Committee of the institutional review board at the Minneapolis Veterans Affairs Medical Center. All subjects gave written informed consent.

Regimens

In a randomized, double-blind, crossover trial, each subject received 240 ml of milk daily with his or her usual breakfast for two one-week periods. The milk preparation was either a 2-percent-fat lactose-hydrolyzed milk or a 2-percent-fat milk (containing a mean of 12.1 g of lactose [0.14 mol per liter; range, 11.8 to 12.5 g]) plus an artificial sweetener (Equal; NutraSweet, Deerfield, Ill.). Subjects were instructed to avoid consuming additional dairy products and other lactose-containing foods. Daily dietary records were kept by the subjects during each experimental period.

Milk Preparation

The lactose in fresh low-fat milk was hydrolyzed by adding 1.07 g of lactase from *Kluyveromyces fragilis* (Lactaid, Pleasantville, N.Y.) to 1 liter of milk (7.9 μmol per liter). Treated milk was incubated for 48 hours at 4°C. No measurable residual lactose remained in the lactose-hydrolyzed milk (<0.05 g per liter [<0.14 mmol per liter]), as determined by an enzymatic assay (Lactose/D-galactose test kit; Boehringer-Mannheim Biochemical, Indianapolis).

The hydrolysis of lactose increases the sweetness of milk. Therefore, the nonhydrolyzed milk was sweetened with aspartame (Equal,

0.82 g per liter [2.8 mmol per liter]). A panel of 30 untrained subjects, not otherwise participating in this study, could not distinguish between the two products in a sensory triangle test (three samples, two of which contained the same product, were presented, and the subject was required to identify the odd sample).¹⁶ Of the total of 90 observations, 41 were correct and 49 were incorrect ($P=0.25$).

Hydrogen and Carbon Dioxide Analysis

The concentrations of carbon dioxide and hydrogen in breath samples were analyzed by gas chromatography¹⁷ (Microlyzer Gas Analyzer, model DP; Quintron Instruments, Milwaukee). The observed hydrogen values were corrected for atmospheric contamination of alveolar air by normalizing the concentrations of observed carbon dioxide to 45 mm Hg, the partial pressure of carbon dioxide in alveolar air. Changes in hydrogen concentrations were calculated by subtracting the hydrogen concentration during fasting from subsequent test values.¹⁸

Reporting of Symptoms

Subjects rated the occurrence and severity of gastrointestinal symptoms experienced during the 24-hour period after each test meal. Bloating, abdominal pain or cramps, and the subjective impression of rectal gas excretion were ranked as follows: 0 indicated no symptoms; 1, trivial symptoms; 2, mild symptoms; 3, moderate symptoms; 4, strong symptoms; and 5, severe symptoms.¹⁹ Diarrhea or loose stool was defined as "an urgent, watery defecation."²⁰ In addition, subjects recorded each passage of flatus.

Statistical Analysis

Data were analyzed by repeated-measures analysis of variance.^{21,22} In addition, because the distribution of the data was skewed, a non-parametric test (McNemar's test) was used to analyze the results. A binomial distribution was used to calculate the two-tailed P value. Individual symptom scores were analyzed separately for each regimen on each day of the study to evaluate the influence of time. Since no differences over time were observed for either regimen, the mean symptom scores for each one-week period were compared.

RESULTS

The breath hydrogen concentrations of the 30 subjects after they consumed 15 g of lactose are shown in Figure 1. The 21 subjects whose breath hydrogen concentrations increased by more than 10 ppm were classified as having lactose malabsorption. The nine subjects with an increase of less than 10 ppm were classified as being able to absorb lactose. Seven of these nine subjects were retested after consuming 10 g of lactulose in 300 ml of water. All seven subjects produced hydrogen in response to lactulose (Fig. 1), confirming the ability of their colonic flora to produce hydrogen.

The 21 subjects with lactose malabsorption included 8 men and 13 women, 18 to 50 years of age, with a mean age of 29.4 years. One was black, seven were Asian, eight were white, and five were Hispanic. The nine who were able to absorb lactose included five women and four men, 18 to 45 years of age, with a mean age of 25.1 years. Eight were white and one was East Indian.

During the two study periods, gastrointestinal symptoms reported by subjects were minimal (mean symptom-severity scores were between 0.1 and 1.2, with 0 indicating no symptoms; 1, trivial symptoms; and 2, mild symptoms). These data are shown in Table 1. The 95

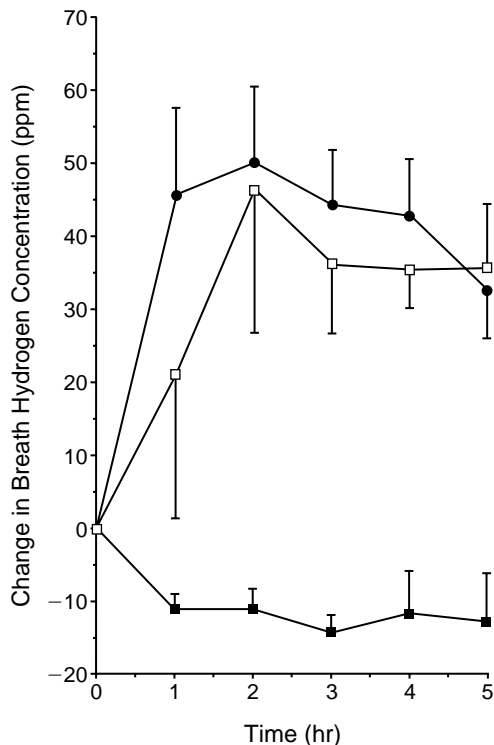


Figure 1. Breath Hydrogen Concentrations of 30 Subjects after the Ingestion of 15 g of Lactose.

Data are expressed as the changes in concentration (means \pm SEM) above the base-line (fasting) values. Twenty-one subjects had lactose malabsorption, as evidenced by sizable increases in breath hydrogen concentration (●), whereas nine subjects had no increase in hydrogen concentration and were considered able to absorb lactose (■). Retesting with 10 g of lactulose of seven of the nine subjects who were able to absorb lactose demonstrated that each responded with a brisk increase in breath hydrogen concentration (□). 1 ppm = 0.045 μ mol per liter.

percent confidence intervals for the differences in mean scores for the symptoms of bloating, abdominal pain, diarrhea, and perceived flatus intensity after the subjects drank ordinary milk and after they drank lactose-hydrolyzed milk include zero. This indicates that the severity of gastrointestinal symptoms was not significantly different in subjects during the two study regimens. In the lactose-malabsorption group, the mean (\pm SEM) difference between regimens in episodes of flatus per day was 2.5 ± 1.1 (95 percent confidence interval, 0.2 to 4.8). A nonparametric statistical test (McNemar's test) showed that regimen was not associated with significant differences in any of these symptoms or in the frequency of flatus (data not shown).

Daily dietary records indicated a high degree of compliance, with no additional sources of lactose reported.

DISCUSSION

If the hydrolysis of lactose in the small bowel is incomplete, lactose is transported to the colon. Colonic bacteria ferment this sugar and produce short-chain fatty acids and gas (hydrogen, carbon dioxide, and methane). The development of diarrhea or gaseous symptoms depends partly on the balance between the production and the removal of these fermentation products. Short-chain fatty acids are rapidly absorbed by the colonic mucosa; diarrhea occurs only when the rate of delivery of lactose to the colon exceeds the rate at which the bacteria ferment lactose.²³ The gases produced during fermentation are consumed by bacteria or are quickly absorbed into the bloodstream.²⁴ Excessive rectal gas or abdominal distention occurs when these disposal mechanisms are overwhelmed. Thus, although even small amounts of lactose are poorly absorbed by people with lactase deficiency, the malabsorption does not necessarily cause appreciable symptoms.

Although many patients are certain that they can link the ingestion of various foods to subsequent abdominal symptoms, it is extremely difficult to pinpoint accurately which, if any, constituents of the diet cause abdominal distress. There is a tendency to attribute symptoms to a food that others have declared to be a problem — for example, lactose or fat. This conclusion is then reinforced by an apparent improvement in symptoms when the food is avoided. Given the enormous placebo effect of dietary manipulations, to document a food intolerance reliably it must be demonstrated that ingestion of the putative offender results in symptoms that do not occur when a "placebo" that appears and tastes identical is ingested. Dou-

Table 1. Gastrointestinal Symptoms and Frequency of Flatus in 30 People with Self-Reported Severe Lactose Intolerance Who Drank 240 ml of Ordinary Milk or Lactose-Hydrolyzed Milk Daily for One Week.*

SYMPTOM	ORDINARY MILK	LACTOSE-HYDROLYZED MILK	DIFFERENCE	95% CONFIDENCE INTERVAL†
Lactose-malabsorption group (n = 21)				
Bloating‡	0.6 \pm 0.1	0.5 \pm 0.1	0.1 \pm 0.1	-0.2 to 0.4
Abdominal pain‡	0.4 \pm 0.1	0.3 \pm 0.1	0.1 \pm 0.1	-0.1 to 0.3
Diarrhea (episodes/day)	0.1 \pm 0.0	0.3 \pm 0.1	-0.2 \pm 0.1	-0.4 to 0.0
Flatus				
Perceived severity‡	1.1 \pm 0.1	0.9 \pm 0.1	0.2 \pm 0.1	0.0 to 0.4
Frequency (episodes/day)	10.1 \pm 1.5	7.6 \pm 1.2	2.5 \pm 1.1	0.2 to 4.8
Lactose-absorption group (n = 9)				
Bloating‡	0.6 \pm 0.2	0.5 \pm 0.2	0.2 \pm 0.2	-0.3 to 0.7
Abdominal pain‡	0.6 \pm 0.2	0.4 \pm 0.2	0.2 \pm 0.1	0.0 to 0.4
Diarrhea (episodes/day)	0.3 \pm 0.2	0.2 \pm 0.1	0.1 \pm 0.2	-0.4 to 0.6
Flatus				
Perceived severity‡	0.9 \pm 0.2	1.2 \pm 0.2	0.3 \pm 0.2	-0.2 to 0.8
Frequency (episodes/day)	11.8 \pm 2.3	8.4 \pm 1.9	3.4 \pm 1.7	-0.53 to 7.3

*Data were analyzed by analysis of variance. Plus-minus values are means \pm SEM.

†The 95 percent confidence intervals for the differences between the means for the severity or presence of symptoms include zero, indicating nonsignificance.

‡Symptoms were ranked according to severity: 0 indicated no symptoms; 1, trivial symptoms; 2, mild symptoms; 3, moderate symptoms; 4, strong symptoms; and 5, severe symptoms.

ble-blind evaluation is virtually impossible with most foods but is possible with lactose.

An uncontrolled study found that 59 percent of 44 lactose-intolerant men experienced symptoms after drinking 240 ml of milk.¹⁰ In contrast, in a series of double-blind studies, Scrimshaw's group found that most people with lactose malabsorption (not selected for the self-reported severity of their intolerance) tolerated 240 ml of a chocolate drink containing 12 g of lactose.¹²⁻¹⁴ Our study extends these observations to people who believed themselves to be extremely intolerant to very small doses of lactose, such as the amounts contained in milk used with coffee or cereal. In addition, we attempted to evaluate the usual pattern of milk ingestion by assessing the severity of a variety of symptoms over a one-week period during which 240 ml of milk was ingested daily. In previous studies that evaluated the responses to single doses of lactose in a chocolate drink,¹²⁻¹⁴ the chocolate may have had an independent effect on symptoms.²⁵ We analyzed each symptom independently, unlike investigators who only reported symptoms as present or absent²⁶ or as the sum of symptom intensity.²⁷

Our finding that 240 ml of milk was not associated with a significant increase in the severity of bloating, abdominal pain, or flatus suggests that people frequently misattribute a variety of abdominal symptoms to lactose intolerance. A larger study might have uncovered some differences. Nevertheless, the symptoms that might be caused by lactose are unlikely to be substantial, particularly in view of the expectation of many subjects before the study that the distress caused by ordinary milk would preclude their completing the study. In most people with lactose malabsorption, the ingestion of 50 g of lactose in a single dose produces symptoms, but that is equivalent to drinking a liter of milk. Future studies should address tolerance of 240 ml of milk consumed throughout the day with meals.

A variety of lactose-digestive aids are available over the counter. Overnight incubation of milk with 5 or 15 drops of a liquid lactase preparation per 240 ml of milk is recommended to produce 70 percent or 100 percent hydrolysis of lactose, respectively. The cost of this treatment, based on the \$7 price of a bottle of the preparation in Minnesota, is about 6 cents per 240 ml of milk (70 percent hydrolysis) or 18 cents per 240 ml (100 percent hydrolysis). Lactase is also available as a tablet that can be taken with a lactose-containing food. The cost of the recommended dose (two tablets) ranges from 30 cents to 60 cents in Minnesota, depending on whether a carton of 100 or 12 tablets is purchased. In many areas, commercially prehydrolyzed milk is available at a cost of about 36 cents per 240-ml serving.

The price of milk in Minnesota is about 19 cents per 240 ml. In our area, the use of lactose-digestive aids increases the cost of milk by a minimum of about 6 cents per 240-ml serving (70 percent hydrolysis of lactose by lactase drops) to a maximum of about 41 cents per 240-ml serving (lactase tablets purchased in small quantities). Although the price of lactose-digestive aids

may vary widely, in our area the minimal additional cost for 100 percent lactose-hydrolyzed milk is about 18 cents per 240 ml (lactase drops). The daily ingestion of 240 ml of such milk entails an annual expenditure of about \$66.

In summary, in a study of 30 people who identified themselves as severely lactose-intolerant, 9 were found to be able to absorb lactose and the other 21, who had lactose malabsorption, tolerated 240 ml of milk a day over a one-week period with minimal, if any, symptoms. We conclude that lactose-digestive aids are not necessary when lactose intake is limited to the equivalent of 240 ml of milk or less a day.

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