Digestive Diseases and Sciences, Vol. 38, No. 11 (November 1993), pp. 2022–2027

Comparative Effects of Exogenous Lactase (β-Galactosidase) Preparations on *in Vivo* Lactose Digestion

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Microbial-derived β-galactosidase (β-gal) enzyme preparations improve in vivo *lactose digestion and tolerance through enhanced gastrointestinal digestion of lactose. Three different β-gal preparations, Lactogest (soft gel capsule), Lactaid (caplet), and DairyEase (chewable tablet) and placebo were fed to lactose maldigesters with either 20 g or 50 g of lactose to compare the efficacy of these products and to further establish a dose–response relationship for use. All enzyme preparations dramatically reduced both the peak and total breath hydrogen production when fed with milk containing 20 g of lactose. Four capsules of Lactogest, two caplets of Lactaid, or two tablets of DairyEase (each treatment containing approx 6000 IU) reduced total hydrogen production significantly ($P < 0.05$) below that observed with two capsules of Lactogest (containing approx 3000 IU) in a stoichiometric manner. Symptoms were significantly ($P < 0.05$) less severe with all the β-gal products. In contrast, with 50 g of lactose in water, peak and total hydrogen production was modestly, but not significantly reduced by the enzyme treatment. Furthermore, symptom scores for bloating, cramping, nausea, pain, diarrhea, and flatus were not different between treatments and the control. The 50-g lactose dose appeared to overwhelm the ability of either 3000 or 6000 IU of β-gal to assist significantly with lactose digestion. Results from these studies demonstrate the relative equivalency of chewable, caplet, and soft-gel β-gal products, based on IUs of enzyme fed.*

KEY WORDS: lactose; lactose maldigestion; lactase; β-galactosidase; lactose intolerance; lactase deficiency.

Lactase (β-galactosidase) enzyme preparations significantly improve *in vivo* lactose digestion and tolerance through enhanced gastrointestinal digestion of lactose (1–8). The efficacy of these products may depend on the dose of lactose and enzyme consumed as well as the activity and survival of the microbial enzyme in the gastrointestinal tract. Thus, the degradation of the carrier (tablet, capsule, or caplet) in the gastrointestinal tract, associated foods and their effect on transit, stomach pH, and bile salt concentrations could influence the efficacy of these products. Recently, several new products have been introduced into the marketplace, formulated as caplets (Lactaid), chewable tablets (DairyEase) or soft gel capsules (Lactogest). Although clinical trials demonstrate the effectiveness of some of these products (1, 5, 7), no direct comparative data are available to guide the health professional and the consumer in selecting the most efficacious

Manuscript received October 14, 1992; accepted October 20, 1992.

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Funded by Thompson Medical Co., Inc. and the Minnesota Agricultural Experiment Station.

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0163-2116/93/1100-2022$07.00/0

preparation. Further, information regarding the effects of different doses of β-galactosidase (β-gal) preparations and doses of lactose on lactose tolerance is limited. Hence, three different β-gal preparations and placebo were fed to lactose maldigesters along with either 20 g or 50 g of lactose in order to compare the effects of these products on lactose digestion and tolerance and to further establish a dose–response relationship for efficacy of use.

MATERIALS AND METHODS

Subjects. Two separate clinical trials were conducted. At the University of Minnesota, 20 healthy subjects (ages 25–40 years, 10 males and 10 females) were classified as lactose maldigesters on the basis of a rise in breath hydrogen concentration to >20 ppm (>1.80 × 10^{-6} g H_2/liter air) after ingestion of 400 ml of low-fat (2%) milk containing approximately 20 g of lactose. At the University of South Alabama, 11 healthy subjects (ages 18–60 years, one male and 10 females) were similarly characterized as maldigesters by breath hydrogen analysis following a 50-g lactose load and by past experience with intolerance symptoms following the consumption of dairy foods. Subjects were excluded from either study if they were pregnant or lactating, had prior gastrointestinal surgery, had illness that would interfere with the experiment, or had used antibiotics within the past 30 days. All subjects consumed each of the five treatments described below in a randomized, double-blinded protocol. The experimental protocols were approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota and Institutional Review Board of the University of South Alabama. Written informed consent was obtained from all subjects prior to initiation of the study.

Treatments. Five treatments were consumed by each subject in random order. At Minnesota these treatments included 400 ml of low-fat (2%) milk containing 20 g of lactose plus; (1) two soft gel vitamin E capsules containing 420 mg/capsule of α-tocopherol in soybean oil as a placebo (Pharmacaps Inc., Elizabeth, New Jersey), (2) two soft gel Lactogest capsules (Thompson Medical Co., Inc., New York, New York), (3) four Lactogest capsules, (4) two Lactaid caplets (Lactaid Inc., Pleasantville, New Jersey) or (5) two chewable DairyEase tablets (Glenbrook Laboratories, New York, New York). β-Gal preparations or the placebo were placed in small brown coded envelopes. Subjects were instructed to swallow the soft-gel capsules and caplets with the first swallows of milk and to chew the DairyEase tablets and swallow the whole tablets with the milk, without observing the contents of the small envelope. A staff member who did not know the code for the products ensured that all subjects complied with the instructions. At the University of South Alabama, the identical protocol was followed except that the five test products were fed with 50 g of lactose dissolved in 200 ml of water.

Hydrogen and Carbon Dioxide Analysis. Lactose maldigestion was assessed by hydrogen analysis of end alveolar breath samples obtained after an overnight (>12 hr) fast and hourly for 8 hr following consumption of the milk plus lactase or placebo treatments according to our standard protocols (7, 9, 10). Only water, black coffee, and black tea were allowed to be consumed during the 8-hr breath collection period. At Minnesota, breath samples were analyzed for hydrogen and carbon dioxide concentrations using gas chromatography (Microlyzer Gas Analyzer, model DP, Quintron Instruments, Milwaukee, Wisconsin, and Alveolyzer, model 24, Quintron Instruments, respectively). The observed hydrogen values were corrected for atmospheric contamination of alveolar air by normalization of the observed carbon dioxide to 45 mm Hg, which is the venous partial pressure of carbon dioxide (11). The changes in hydrogen concentrations (Δ ppm) were calculated by subtracting fasting hydrogen values from subsequent test values. At South Alabama, breath samples (obtained at 30-min intervals by a Quintron GaSampler, Milwaukee, Wisconsin) were also analyzed for hydrogen using gas chromatography (Microlyzer, model 12, Quintron Instruments). No correction was made for carbon dioxide or initial hydrogen concentrations (7). Alabama patients had all food and fluids proscribed for the 12 hr prior to and during the 8-hr collection periods.

TABLE 1. β-GALACTOSIDASE STUDY OF PRODUCTS

Product	*Lot #*	*FCC units**
Lactaid	(L) 11	2733/caplets
Lactogest	49177	1459/capsules
DairyEase	5007FF	2895/tablets

*The lactase products were analyzed at pH 4.5 (acetate buffer) according to the FCC III method. Data are the average of duplicates.

Symptom Assessment. At Minnesota, all subjects kept a dairy of symptoms and self-rated gas, stomach pain and/or cramps and diarrhea and/or loose stool on a 0–5 (none to severe) scale for each hour from 0 to 8 hr following the test meal. At South Alabama, all subjects kept a similar diary, except that symptoms of bloating, abdominal cramps, nausea, abdominal pain, diarrhea and gas were self-scored by subjects at baseline and 4 and 8 hr on a 1–5 scale (none to worst ever experienced).

β-Galactosidase Activity of Enzyme Preparations. The β-gal activities of the enzyme preparations were measured according to the FCC III method (12) in duplicate from the same lots used in the feeding trials. Measurements were made using acetate buffer at pH 4.5 (12).

Statistical Analysis. Individual summed hydrogen values and symptom data were analyzed by analysis of variance. The sums of hourly breath hydrogen concentrations following consumption of the placebo or test products were used for group comparisons (13). The least significant difference test was used to compare means (14).

RESULTS

Minnesota Data. β-Gal activities of the lactase products are shown in Table 1. The dose of four

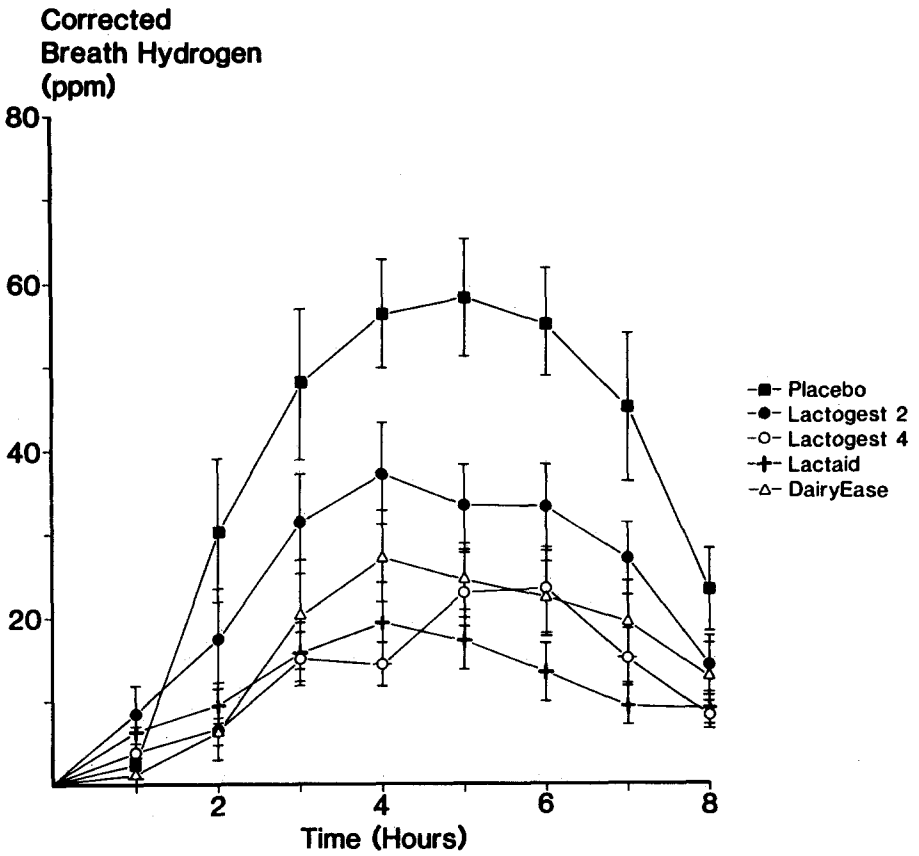

Fig 1. Breath hydrogen production (ppm) following consumption of 400 ml of 2% low-fat milk with β-galactosidase products and placebo. Data are expressed as mean values ± SEM for 20 lactose maldigesting subjects.

Lactogest capsules is equivalent to two Lactaid caplets or DairyEase tablets. Breath hydrogen production over the 8 hr following the administration of the treatment products with 400 ml of low-fat (2%) milk is shown in Figure 1. As expected, the placebo resulted in a large increase in breath hydrogen, peaking at Δ 58 ppm at 5 hr after consumption. All enzyme preparations dramatically reduced both hydrogen production quantified by the sum of the hourly hydrogen concentrations (Table 2). However, four capsules of Lactogest, two caplets of Lactaid, or two tablets of DairyEase reduced total hydrogen production significantly below that observed with two capsules of Lactogest ($P < 0.05$) in a fairly stoichiometric manner; twice the enzyme activity resulted in approximately one half the hydrogen production.

Total symptoms (mean sum of all symptom scores over the 8-hr period) were significantly improved with the β-gal products (Table 3). All products caused mean symptom scores to be reduced by at least one half. Most of the symptom scores were attributable to excessive flatulence, which was also reduced significantly. Stomach pain and diarrhea occurred less frequently. Stom-

TABLE 2. COMPARISON* OF SUMMATION OF HOURLY BREATH HYDROGEN CONCENTRATIONS FOLLOWING CONSUMPTION OF β-GALACTOSIDASE PRODUCTS WITH 400 ML OF LOW-FAT MILK (MINNESOTA) OR 50 G LACTOSE DISSOLVED IN 200 ML OF WATER (SOUTH ALABAMA)

	Minnesota hydrogen (ppm)	*Homogenous groups†*	*South Alabama Hydrogen (ppm)‡*
Placebo, 2 capsules	320.3	I	435.4
Lactogest, 2 capsules	205.1	I	457.9
DairyEase, 2 tablets	133.3	I I	391.4
Lactogest, 4 capsules	114.6	I I	332.5
Lactaid, 2 caplets	102.1	I	368.3

*Least significant difference pairwise comparisons.
†Treatments not sharing Is in the same column are statistically different ($P < 0.05$).
‡P = NS.

TABLE 3. COMPARISON* OF SYMPTOMS FOLLOWING CONSUMPTION OF β-GALACTOSIDASE PRODUCTS WITH 400 ML OF (2%) LOW-FAT MILK

Treatment	*Mean of symptom scores†*	*Homogeneous groups‡*	*Mean of gas scores*	*Homogeneous groups*	*Mean of stomach pain scores*	*Homogeneous groups*	*Mean of diarrhea scores*	*Homogeneous groups*
Placebo, 2 capsules	10.45	I	7.85	I	1.55	I	1.30	I
Lactogest, 2 capsules	4.75	I	2.95	I	1.30	I I	0.25	I
DairyEase, 2 tablets	2.75	I I	2.25	I	0.35	I I	0.15	I
Lactaid, 2 caplets	2.60	I I	2.10	I	0.35	I I	0.15	I
Lactogest, 4 capsules	1.25	I	1.00	I	0.20	I	0.05	I

*Least significant difference pairwise comparisons.
†Symptom scores are expressed as the mean of the sum of scores rating symptoms from 0 (none) to 5 (severe) for each hour from baseline to 8 hr after the challenge.
‡Treatments not sharing Is in the same column are statistically different ($P < 0.05$).

ach pain was significantly reduced only with the higher doses of the lactase preparations, whereas all products and/or doses significantly reduced the score for diarrhea.

South Alabama Data. Mean hydrogen production from the β-gal products consumed with 50 g of lactose in water are shown in Figure 2. Although hydrogen production was modestly reduced by the enzyme treatment, no significant differences between treatments were observed ($P = 0.65$ for peak production and $P = 0.77$ for the sum of hourly productions, Table 2). Further, symptom scores for bloating, cramping, nausea, pain, diarrhea, and flatus were not significantly different between treatments and the control (Table 4). The large lactose dose appeared to overwhelm the ability of either 3000 or 6000 units of β-gal to assist significantly with lactose digestion.

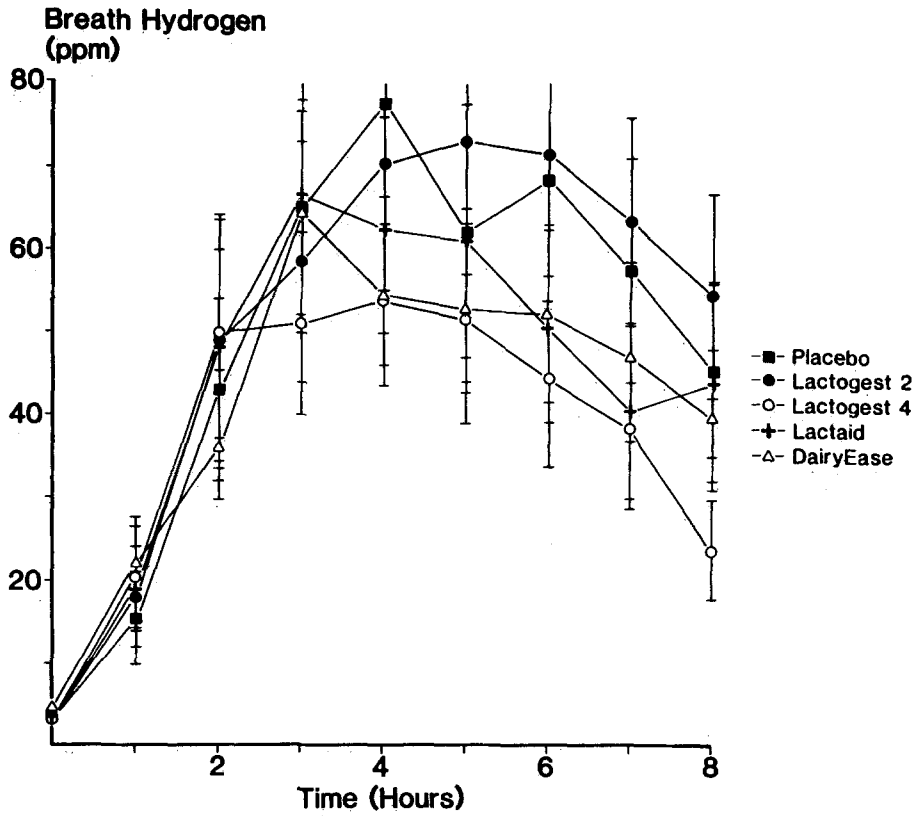

Fig 2. Breath hydrogen production (uncorrected) following consumption of 50 g of lactose dissolved in 200 ml water with β-galactosidase products and placebo. Data are expressed as mean values and SEM for 11 lactose maldigesting subjects.

TABLE 4. COMPARISON OF SYMPTOMS FOLLOWING CONSUMPTION β-GALACTOSIDASE PRODUCTS WITH 50 G POWDERED LACTOSE IN 200 ML WATER*

	Placebo† (2 capsules)	*Lactogest (2 capsules)*	*Lactogest (4 capsules)*	*DairyEase (2 tablets)*	*Lactaid (2 caplets)*
Bloating	4.1	4.4	4.0	4.6	5.2
Cramps	2.7	3.5	3.3	3.0	3.3
Nausea	2.8	2.3	2.4	2.2	2.4
Pain	3.0	2.5	3.2	3.4	3.1
Diarrhea	2.9	3.4	2.5	2.6	3.2
Flatus	4.8	5.4	4.7	5.6	6.1
Number of stool motions‡	1.2	2.1	0.9	1.7	2.1

*Symptom scores are expressed as the sum of mean scores rating symptoms from 1 (none) to 5 (worst ever experienced) at baseline and 4 and 8 hr after challenge.
†P = NS for all symptom variables.
‡Number of stool motions during the study period.

DISCUSSION

Results from these studies demonstrate the relative equivalency of soft-gel, caplet, and chewable capsule products, based on IUs of enzyme activity fed. Physicians, dietitians, and the consumer may be advised to recommend or choose an appropriate product based not on its efficacy per unit of enzyme activity, but rather on form and price. It appears that in the range of 20 g of lactose consumed, 6000 IU of activity is sufficient to dramatically improve digestion and tolerance for most lactose maldigesters. Further, in this range of lactose consumption (the amount contained in 400 ml or approximately 14 oz of milk), there appears to be a stoichiometric response of hydrogen gas production to the consumption of β-gal. Doubling the β-gal dose will half the amount of gas produced.

In contrast to the results obtained with 20 g of lactose in milk, 50 g of lactose in water appeared to overwhelm the ability of 3000 or 6000 IU of β-gal products to improve digestion or tolerance. This finding is probably attributable to both the greater substrate concentration and the more rapid transit that occurred due to consumption of lactose with water rather than with other milk components, thus reducing the time allowed for luminal digestion of lactose. Hydrogen concentration rose fairly linearly with both doses, peaking at 5 hr with the milk feeding and at 4 hr with the lactose in water, suggesting only a small effect on transit. However, differences in the populations studied, the source and dose of the lactose used, and the evaluation of symptoms make any direct comparison of the data from the two studies (Minnesota and Alabama) inappropriate.

Although it may be speculated from these results that a linear relationship exists between the dose of lactose and the units of β-gal required to improve digestion, the contribution of residual mucosal lactase activity to lactose digestion must be considered. The contribution of residual mucosal lactase to overall lactose digestion is probably in the range of 50% of a 20-g dose (11), based on controlled studies of hydrogen production from lactulose (which is totally nondigested by mammalian lactase) and lactose. Recently, Brand and Holt (15) reported that small doses of lactose do not result in appreciable breath hydrogen production, presumably due to intestinal hydrolysis. A 300 ml dose of a 50% lactose-reduced milk (containing 7.2 g lactose) resulted in no more gas than was observed with 80–95% lactose-reduced milk (containing 3 g or <0.75 of lactose, respectively). Unfortunately, the physiological importance of and variation in residual lactase activity are not well characterized, but may be additional critical factors in explaining variation in the intolerance symptoms experienced by lactose maldigesters.

ACKNOWLEDGMENTS

We acknowledge clinical support by Dr. Afifa Halim and Ms. Suzanne Sims, RN, of the Clinical Investigation Section, and administrative assistance by Suzanne G. Williams, RN, MSN, gastroenterology research assistant, both at the University of South Alabama.

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