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EFFECT OF LACTASE PREPARATIONS IN ASYMPTOMATIC INDIVIDUALS WITH LACTASE DEFICIENCY – GASTRIC DIGESTION OF LACTOSE AND BREATH HYDROGEN ANALYSIS –

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ABSTRACT

We compared two lactase preparations derived from *Aspergillus orizae* (AOL) and *Penicillinase multicolor* (PML) for stability in the stomach and overall enzymatic activity in 10 asymptomatic subjects with lactase deficiency. The subjects were given 10,000 FCC units of either AOL or PML 30 min prior to or simultaneously with 300 ml of milk. Gastric juice was withdrawn through a nasogastric tube immediately after and every 15 min for 60 min, and breath was sampled before and every 15 min for 6 h after the milk ingestion. When lactase was given simultaneously with the milk, gastric juice lactase activity and galactose concentration were significantly higher than the control levels. When lactase preparations were given 30 min prior to the milk, neither lactase activity nor galactose was detected in the gastric juice. The pH of the gastric juice was about 6.0 after the milk ingestion. Breath hydrogen did not increase when milk was ingested simultaneously with enzymes, but did increase if enzymes were given 30 min prior to milk ingestion. There were no significant differences in lactase activity, galactose concentration in gastric juice, or breath hydrogen when AOL and PML were compared. In conclusion, with exogenous lactase, digestion of lactose begins in the stomach when pH is raised to 6.0 by the buffering action of milk. Lactase preparations are effective assessed by breath hydrogen analysis in asymptomatic individuals with lactase deficiency if the enzymes are given simultaneously with milk.

Key Words: lactase deficiency, lactose intolerance, galactose, lactase, breath hydrogen

INTRODUCTION

Average milk intake in Japan and probably in other Asian countries is extremely low. We have shown previously[1] that average consumption of milk is 200 ml per day among Japanese, which is 1/3 the amount consumed by Americans. Since we have many patients with osteoporosis, we recommend a diet richer in milk for its calcium content. The problem is, however, that almost all Japanese and Asians are lactase deficient.[1] While 20% of Japanese are lactose intol-

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erant, others generally without symptoms cannot tolerate large amounts of milk.[1,2] To increase milk intake in our population, it is necessary to adopt some means to reduce the lactose content in milk. Prehydrolyzed milk with lactase is available in Japan, but it is not popular because of its sweet taste and limited availability. Several lactase preparations are available that require a medical prescription. The most practical way of making lactase preparations widely available may be to sell them on an over-the-counter (OTC) basis. However, the effectiveness of lactase preparations has not been studied in asymptomatic lactase-deficient subjects.

Enzymes including lactase have an optimal pH for activity. Many lactase preparations act optimally at pH 5.0,[3,4] which is close to postprandial gastric pH.[5] We have recently shown that lipase preparations taken with a meal start to act from the early gastric phase, probably because postprandial gastric pH rises to the optimal pH of lipase.[6] If the same is true for lactase, gastric digestion of lactose will start from the stomach. If we give a lactase preparation that is stable at a lower pH, the preparation could remain active in the stomach in the fasting state, long before lactose-containing food products are ingested.

In the present study, we addressed the three following questions: Do lactase preparations stable at a relatively low pH remain active in the stomach for a relatively long period of time? Does gastric digestion of lactose occur as a result of the lactase preparation? Are lactase preparations effective in asymptomatic subjects with lactase deficiency?

SUBJECTS AND METHODS

Subjects

Ten people volunteered as study subjects. They were divided into two groups of five each. The first group (1 woman and 4 men, 23 to 25 years of age) was designated for gastric digestion study. The other group (2 women and 3 men, 20 to 42 years of age) was designated for breath hydrogen analysis. All subjects were healthy, had no history of gastrointestinal disease, and had not used any antibiotic for at least 3 months. In preliminary experiments, subjects were given 300 ml of milk, which contains about 18 g of lactose, and showed breath hydrogen levels of over 20 ppm. They tolerated ingestion of 300 ml of milk well and reported no subjective symptoms. The subjects were considered lactase deficient but not lactose intolerant.[7] Written informed consent was obtained from all subjects, and the study was approved by the Human Research Committee of the Research Center of Health, Physical Fitness and Sports, Nagoya University.

Methods

The lactase preparations used in this study were based on lactase produced by *Aspergillus orizae* or *Penicillium multicolor* (AOL and PML, respectively); both were generously supplied by Amano Enzyme Co. (Gifu, Japan). The characteristics of the enzymes are given in Table 1.

Table 1. Characteristics of lactase from *A. oryzae* and *P. multicolor*

	A. oryzae	*P. multicolor*
Optimum pH	5.0	5.0
pH stability	4.0–7.0	2.5–7.0
Optimum temperature	50°C	60°C
Thermal stability	< 50°C	< 60°C
Km for lactose	0.035 mol/L	0.011 mol/L

Both preparations (10,000 FCC units) were dissolved with 10 ml of distilled water before administration. The dose of the lactase preparations was determined from the *in vitro* study as that to digest about 18 g of lactose. In the gastric digestion experiment, 34.2 g of skim milk powder containing 18.3 g of lactose was dissolved in 300 ml of distilled water. In the breath hydrogen analysis experiment, 300 ml of non-skimmed milk was used.

Gastric digestion protocol

This study was conducted using a crossover design. After subjects fasted overnight, a nasogastric tube was inserted and they participated in one of the following tests: AOL given 30 min prior to milk ingestion; AOL given with milk; PML given 30 min prior to milk ingestion; PML given with milk; maltodextrin given with milk (as a control).

Ten milliliters of gastric juice was aspirated immediately after the subject swallowed the milk and every 15 min thereafter for 60 min. The pH of the gastric juice was determined and the specimen was divided into two parts of 5 ml each. One sample was used to determine lactase activity, which was measured by the FCC method at pH 4.5 with O-nitrophenol-β-D-galactopyranoside as a substrate. The other sample was used for galactose and HPLC analysis for mono- and di-saccharides. Enzymatic activity was inactivated by addition of 0.15 ml of 6N HCl in these samples. Galactose was measured with galactose test kits (Boehringer Mannheim, Tokyo). For HPLC analysis, 2.0 ml of acetonitrile was added and mixed to 0.5 ml of a 5-fold distilled water dilution of the supernatant obtained by centrifuging the inactivated enzyme samples. The mixture was put through a membrane filter and 30 μl of the filtrate was used for analysis. Since we did not know the actual gastric volume at any given time, mono- and disaccharide values were divided by the original lactose value and showed as the percentage remaining in the stomach. Lactase activity and galactose concentrations were standardized by this rate.

Breath hydrogen analysis

After an overnight fast, subjects were subjected to the same protocol as that for the gastric juice analysis. Breath samples were collected in a commercially available collection bag before milk ingestion and every 15 min after ingestion for 6 h. Lunch (a 100 g hamburger patty with coffee or tea) was provided at 4 h after the test was started. Hydrogen was measured with a gas chromatograph (MicroLyzer model 12i, Quintron Instruments, Milwaukee, WI, USA). The area under the curve (AUC) was calculated from the time breath hydrogen increased by 3 ppm over the baseline (oro-cecal transit time; OCTT) until the end of the experiment. Since the OCTT varied from subject to subject, the AUC was expressed per hour.

Statistical analysis

Data are expressed as mean ± standard error. The paired *t*-test was used for paired data and Bonferroni's method was applied after analysis of variance (ANOVA) for multiple comparisons.

RESULTS

Gastric digestion

When lactase was given simultaneously with milk, lactase activity and galactose concentrations in gastric juice were significantly higher than under control conditions (Figs. 1 and 2). Lactase activity then decreased gradually to the control level. Galactose concentration increased to a maximum by 15 min and remained high. There were no significant differences in lactase

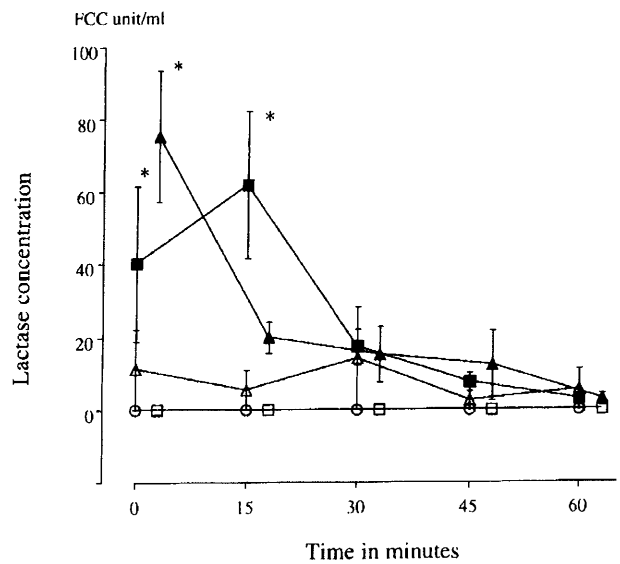

Fig. 1 Lactase activity in gastric juice. Mean ± SE values are shown. Open squares and open triangles indicate lactase from *A. orizae* (AOL) and *P. multicolor* (PML), respectively, given 30 min prior to milk ingestion, and solid squares and solid triangles indicate AOL and PML, respectively, given simultaneously with milk ingestion. Open circles indicate control values. (* $p < 0.05$ vs. control)

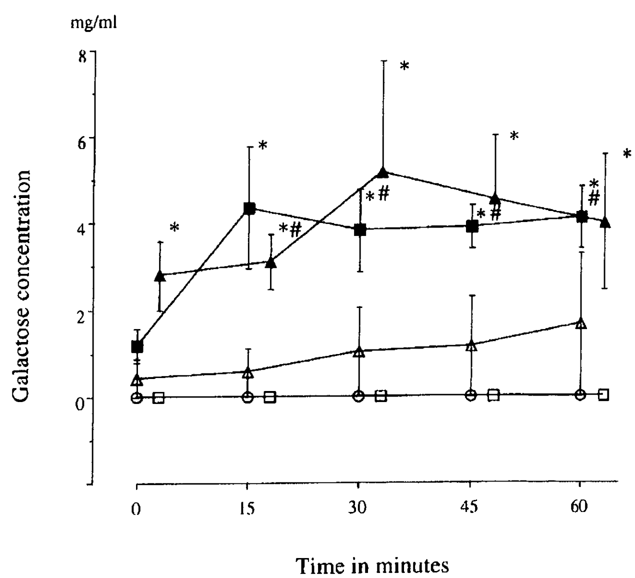

Fig. 2 Galactose concentrations in gastric juice. Mean ± SE values are shown. Open squares and open triangles indicate lactase from *A. orizae* (AOL) and *P. multicolor* (PML), respectively, given 30 min prior to milk ingestion, and solid squares and solid triangles indicate AOL and PML, respectively, given simultaneously with milk ingestion. Open circles indicate control values. (* $p < 0.05$ vs. control and # $p < 0.05$ vs. time 0)

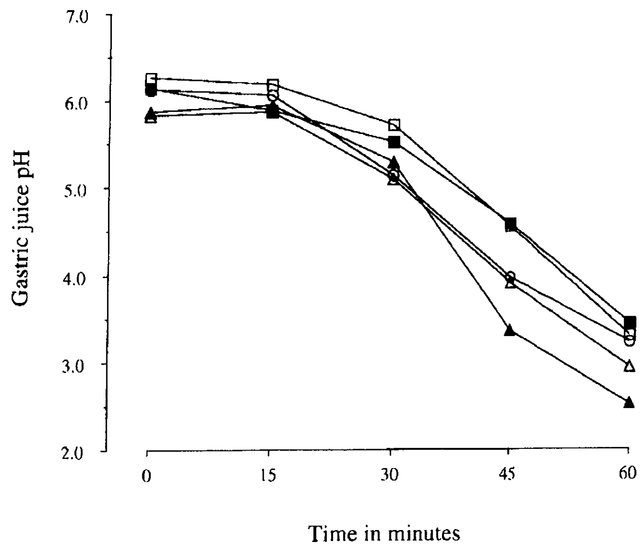

Fig. 3 pH of gastric juice. Only mean values are shown. Open squares and open triangles indicate lactase from *A. orizae* (AOL) and *P. multicolor* (PML), respectively, given 30 min prior to milk ingestion, and solid squares and solid triangles indicate AOL and PML, respectively, given simultaneously with milk ingestion. Open circles indicate control values.

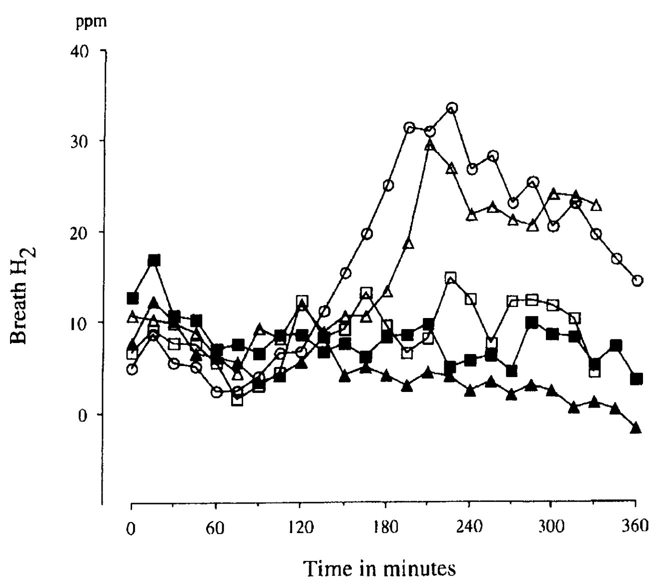

Fig. 4 Breath hydrogen concentrations. Only mean values are shown. Open squares and open triangles indicate lactase from *A. orizae* (AOL) and *P. multicolor* (PML), respectively, given 30 min prior to milk ingestion, and solid squares and solid triangles indicate AOL and PML, respectively, given simultaneously with milk ingestion. Open circles indicate control values.

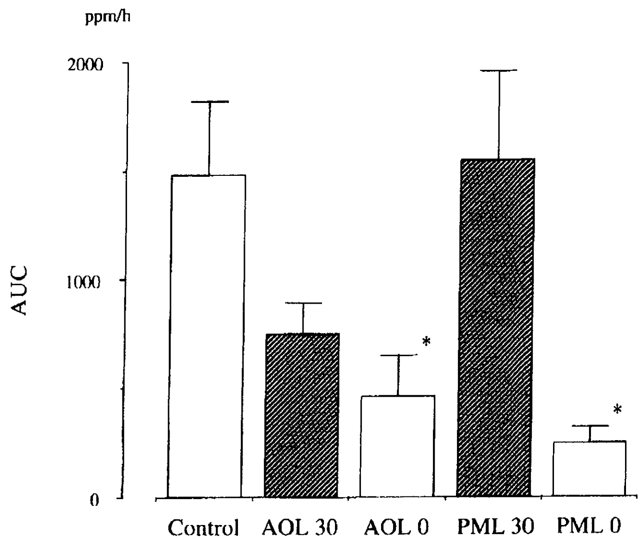

Fig. 5 The area under the curve. AOL 30 and PML 30 represent lactase from *A. orizae* and *P. multicolor*, respectively, given 30 min prior to milk ingestion. AOL 0 and PML 0 represent AOL and PML, respectively, given simultaneously with milk ingestion. (* $p < 0.05$ vs. control)

activity or galactose concentrations when AOL and PML were compared. When the lactase preparations, either AOL or PML, were given 30 min prior to the milk, lactase activity and galactose were not detected in the gastric juice. The gastric juice pH increased to 6.0 (mean; 5.8 – 6.3) soon after the ingestion of milk, remained high for at least 30 min, and then slowly decreased to below 4.0 (mean; 2.5 – 3.4) at 60 min (Fig. 3). There were no significant differences in pH values between any of the subjects under any condition.

Breath hydrogen

The breath hydrogen concentration did not increase when AOL or PML was given simultaneously with milk (Fig. 4). The AUC per hour was significantly lower when AOL or PML was given simultaneously with milk than in the control condition ($p<0.05$, Fig. 5). When lactase preparations were taken 30 min prior to the ingestion of milk, the breath hydrogen concentration increased and the AUCs did not differ from the AUC in the control condition. There was no significant difference in the AUCs between the preparations with AOL and PML.

DISCUSSION

The lactase preparations used in this study were derived from *A. oryzae* and *P. multicolor*. Both lactase preparations have similar enzymatic characteristics, such as an optimal temperature and pH for activity, and temperature stability. The pH stability, however, differs somewhat, in that PML is stable between 2.5 and 7.0 and AOL between 4.0 to 7.0. Because of this difference, it is possible that PML survives longer than AOL in the acidic gastric juice. In the present experiment, however, both enzymes lost their activity when administered 30 min prior to the milk ingestion. The pH in the fasting gastric juice might have been below 2.5, but this was not measured. In our previous study with 84 subjects, fasting gastric juice pH in subjects younger than 40 years old was 1.3 to 2.1.[8] Biller *et al.*[9] suggested that lactase from *A. oryzae* might be more effective than that from *Kluveromyces lactis* because of its increased stability over wider ranges of pH and temperature. However, they studied children with lactose intolerance, and the pH of gastric juice may be higher in children than in adults.

In an *in vitro* study, AOL but not PML lost its activity within 30 min in an acidic environment. Thus, we chose administration 30 min before as well as immediately before milk ingestion. Since both enzyme preparations given 30 min prior to milk ingestion became inactive, it does not seem necessary to conduct a further study with a longer period before milk ingestion.

The digestion of lactose by exogenous lactase starts from the gastric phase. This is analogous to lipid digestion by exogenous lipase. If we give lipase with a fatty meal, fat digestion starts in the stomach and the meal empties faster from the stomach.[1] In this study, pH in the stomach increased to 6.0 after milk ingestion, creating an ideal environment for lactase activity. If lactase is given simultaneously with milk, pH stability is not a major problem in gastric digestion of lactose.

It is well documented that lactase preparations are effective for patients with lactose intolerance.[3,4,9-13] From our breath hydrogen data, it seems reasonable to consider that milk will not cause symptoms in the subjects with lactose intolerance if sufficient amounts of lactase preparation are given. The dose should be 10,000 FCC units for 300 ml of milk. The effectiveness of lactase preparations, however, given to individuals with lactase deficiency but no gastrointestinal symptoms is not well demonstrated. Since there are no symptoms, it has been difficult to assess the effect of lactase preparations. With breath hydrogen analysis, it becomes possible to assess the effect of lactase preparations in such persons. When undigested lactose in milk enters the colon it is rapidly fermented to short chain fatty acids by colonic bacteria, liberating CO_2, hydrogen, and, in some people, methane. The hydrogen diffuses into the blood and is exhaled in the breath. Thus, after ingestion of milk, measurement of hydrogen concentration of the breath indicates the amount of lactose that has entered the colon. As expected, both our lactase preparations were effective when they were given simultaneously with milk. They were ineffective when given 30 min prior to the milk.

About 20% of the population in Japan is lactose intolerant.[1,2] The majority of Japanese are lactase deficient but display no clinical symptoms.[1,2] Breath hydrogen in all subjects in our study increased over 20 ppm after ingestion of 300 ml of milk, thus indicating lactase deficiency.[7] The average milk intake of adults in Japan is about 200 ml per day, which is far less than that of Europeans and Americans. Usually 75% of an individual's calcium is obtained from dairy products. In the Japanese, calcium intake is very low in terms of the daily nutritional requirement. Thus, it is suggested by many nutritionists as well as in the mass media that Japanese should consume more milk to prevent osteoporosis. Since the Japanese and others who are lactase deficient cannot tolerate large amounts of milk, milk should be taken with lactase preparations in one form or another. Although administration of lactase preparations may increase milk intake in asymptomatic lactase deficient subjects, there are no data demonstrating this to our knowledge. To increase milk intake, however, administration of lactase preparations may be the best choice. Any type of lactase preparation will be useful if taken simultaneously with milk, and such preparations should be provided on an OTC basis to increase individual milk intake in countries like Japan.

In conclusion, digestion of lactose starts from the stomach by exogenous lactase when pH is raised to 6.0 by the buffering action of milk. Lactase preparations are effective for asymptomatic individuals with lactase deficiency if taken simultaneously with milk.

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Oral supplements to improve lactose digestion and tolerance / Aportes orales para mejorar la digestión y la tolerancia de la lactosa

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Oral supplements to improve lactose digestion and tolerance

Aportes orales para mejorar la digestión y la tolerancia de la lactosa

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There are two principal microbial sources of β-galactosidase (lactase): (*i*) yeast (*Kluyveromyces lactis*) and (*ii*) fungi (*Aspergillus niger* and *A. oryzae*). From these sources, several over-the-counter lactase supplements have been prepared and introduced into the US market. Controlled clinical trials have shown that these lactose digestive aids are effective. However, the results have been variable. A consistent observation in many of these is that there may be a subpopulation with very low levels of endogenous residual lactase. These people might need much higher levels of oral supplements than currently recommended. Generally, the products are expensive and research should be directed toward reducing the cost of these oral supplements.

Keywords: lactose, maldigestion, lactase, β-galactosidase, enzymes

Las dos fuentes principales de β-galactosidasa (lactasa) son: (i) las levaduras (*Kluyveromyces lactis*) y (ii) los hongos (*Aspergillus niger* y *A. oryzae*). A partir de estas dos fuentes se han elaborado preparados de lactasa que no precisan prescripción médica y que se han introducido en el mercado americano. Mediante pruebas clínicas de control se ha puesto de manifiesto la efectividad de estos productos, aunque los resultados son variables. Concretamente, en estas pruebas se ha observado que podría haber un grupo de población con niveles muy bajos de lactasa residual endógena. Estas personas necesitarían aportes administrados oralmente más grandes de lo comunmente recomendado. Generalmente, el costo de estas formulaciones es alto y la investigación debería dirigirse hacia el estudio de cómo abaratar su producción.

Palabras clave: lactosa, indigestión, lactasa, β-galactosidasa, enzimas

INTRODUCTION

Primary lactase deficiency is a genetically programmed event and develops in a vast majority of humans by adulthood (Simoons, 1970; Sahi, 1994). Of several enzymes and complexes thereof located in the brush border of small intestinal epithelial cells, β-galactosidase (EC 3.2.1.23) or lactase, hydrolyses the milk sugar lactose. Hydrolysis of lactose into its constituent monosaccharides is a prerequisite for absorption of lactose. Thus, hypolactasia may become evident as lactose intolerance symptoms after consumption of lactose or milk (Rao *et al.*, 1985; Sahi, 1994). Lactose intolerance symptoms generally include flatulence, bloating, abdominal cramps and, in severe intolerance cases, diarrhoea. Lactose intolerant subjects, therefore, avoid foods containing lactose, which might compromise the intake of many important nutrients, especially calcium.

Exogenous supplementation of the enzyme β-galactosidase to mitigate symptoms of lactose intolerance was advocated by Kobayashi *et al.* (1975). In fact, the concept of exogenous supplementation of digestive enzymes was practiced much earlier, especially for

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Table 1. Commercial lactase preparations.

Tabla 1. Preparados de lactasa comerciales.

Source	Product	Supplier
Kluyveromyces lactis (optimum pH 6.8–7.0 optimum temp. 35–37 °C)	Lactaid	SugarLo Co.,Inc. Pleasantville, NJ, USA
	Maxilact LX 5000	Gist-Brocades NV Holland
	Lactozyme	Novo Industries Inc. Bagswaerd Denmark
Aspergillus sp. (optimum pH 3.0–7.0, optimum temp. 55 °C)	Lactase N (from *A. niger*)	GB Fermentation Products Co. Kingstree, SC, USA
	Lactase A (Takamine: from *A. oryzae*)	Miles Laboratories Elkhart, IN, USA
	Milk digestant (from *A. niger*)	Malabar Forumula, Cypress, CA, USA

Table 2. Commercial-over-the-counter lactose digestive aids.

Tabla 2. Preparados comerciales para la digestión de la lactosa de venta sin prescripción medica.

Source	Product	Supplier
Kluyveromyces lactis	Lactaid caplets	Lactaid, Inc. Pleasantville, NJ, USA
Aspergillus niger	Dairy Ease chewable tablets	Glenbrook Laboratories New York, NY, USA
Aspergillus oryzae	Lactrase capsules	Schwarz Pharmaceuticals Milwaukee, WI, USA
	Lactogest soft gel capsules	Thompson Medical Co., Inc. New York, NY, USA

with pancreatic enzymes. Rand (1981) reported an alleviation in lactose intolerance when milk was consumed along with enteric-coated β-galactosidase embedded in algin beads. Likewise, Mizote *et al.* (1978) successfully reduced diarrhoea in gastrectomized patients with lactase supplementation. Systematic studies for the sole purpose of helping lactose intolerant populations, however, were started by Solomons *et al.* (1982) in Guatemala. They demonstrated a 37% reduction in colonic lactose fermentation when β-galactosidase was added to milk prior to its consumption. This brief review focuses on the current available lactase replacement therapy strategies

LACTASE SUPPLEMENTS

Lactase preparations

Several enzyme preparations are available for substitution therapy for lactose maldigestors (Table 1) Two principal sources of food grade lactase are currently available: lactase from yeast, *Kluyveromyces lactis*, has optimum activity around neutral pH with maximum activity around 37 °C; lactase from the fungi *Aspergillus niger* or *A. oryzae* have optimum activity in an acidic environment with maximum activity at 55 °C. Table 2 lists the over-the-counter lactose digestive aids (enzymes) currently available.

Human studies with commercial oral supplements

The feasibility of effective enzyme replacement therapy for lactose intolerant individuals was demonstrated by Rosado *et al.* (1984). Figure 1 shows

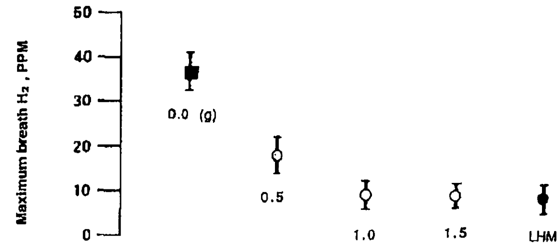

Figure 1. Breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactaid) from *Kluyveromyces lactis* added to 360 ml of milk 5 min before consumption ($n = 13 \pm$ SEM). LHM, lactose hydrolysed milk (from Rosado *et al.*, 1984 with permission).

Figura 1. Hidrógeno eliminado en la respiración en función de cantidades crecientes de β-galactosidase (Lactaid) añadida a 360 ml de leche 5 minutos antes de su ingestión ($n = 13$ $\pm$ SEM). LHM, leche con lactosa hidrolizada (datos según Rosado *et al.*, 1984).

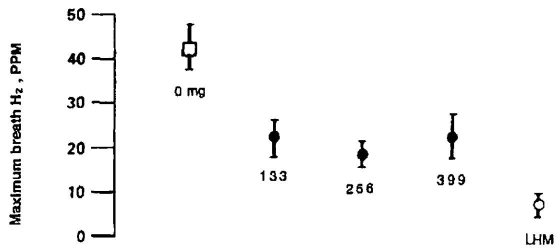

Figure 2. Breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactase N) from *Aspergillus niger* added to 360 ml of milk 5 min before consumption ($n = 13 \pm$ SEM). LHM, lactose hydrolysed milk (from Rosado *et al.*, 1984, with permission).

Figura 2. Hidrógeno eliminado en la respiración en función de cantidades crecientes de β-galactosidase (Lactase N) de *Aspergillus niger* añadida a 360 ml de leche 5 minutos antes de su ingestión ($n = 13$; $\pm$ SEM). LHM, leche con lactosa hidrolizada (datos según Rosado *et al.*, 1984).

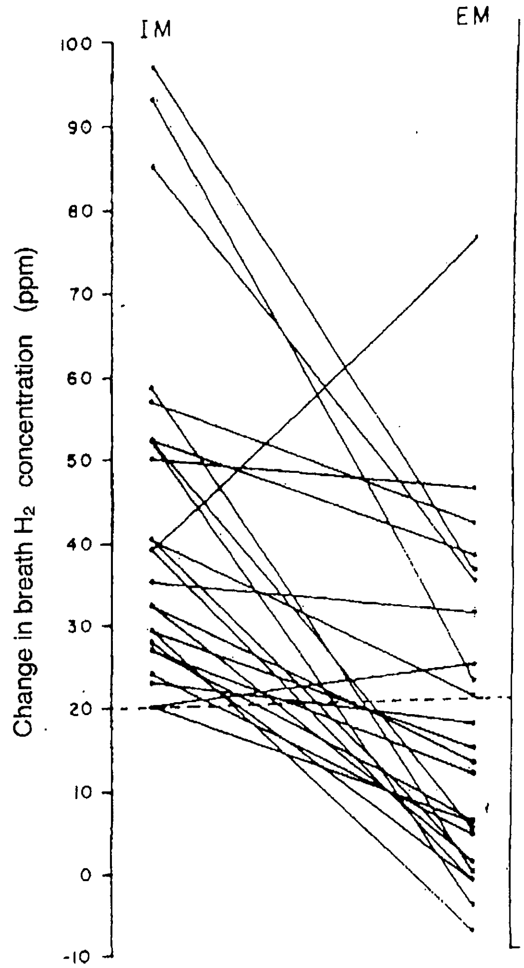

Figure 3. Change in breath hydrogen concentration in 25 lactose maldigestors after consuming intact milk (IM) or milk with added enzyme (EM), containing 1 g of Lactaid or 1.8 g of lactase (from Rosado *et al.*, 1984, with permission).

Figura 3. Variación de la concentración de hidrógeno eliminado en la respiración en 25 individuos con mala digestión de lactosa después de ingerir leche intacta (IM) o con adición de enzimas (EM), conteniendo 1 g de Lactaid o 18 g de lactasa (datos según Rosado *et al.*, 1984).

maximum breath hydrogen excretion as a function of consumption of graded levels of β-galactosidase (Lactaid) added to 360 ml of milk, 5 min before consumption by 13 lactose malabsorbers. Addition of 0.5 g of Lactaid to milk reduced peak hydrogen excretion substantially. Increasing the level of Lactaid further reduced the levels of breath hydrogen excretion (Figure 1). However, with 1.0 g of Lactaid, 23% of individuals still showed a maximum increase in breath hydrogen concentration of $\geqslant 20$ ppm; similarly with a 1.5 g dose, 15% of subjects had a positive breath hydrogen test result. Figure 2 shows the mean

Table 3. Number of subjects reporting symptoms of lactose intolerance after consuming two preparations of lactase added to 360 ml of milk 5 min before consumption. Data from Rosado *et al.* (1984); $n = 13$

Tabla 3. Número de individuos que presentaron síntomas de intolerancia a la lactasa después de consumir dos preparados de lactasa, añadidos a 360 ml de leche 5 minutos antes de su ingestión (según datos de Rosado *et al.*, 1984; $n = 13$).

Lactase preparation	Dose Lactaid (g)/Lactase N (mg)				
	0.0/0.0	0.5/133	1.0/266	1.5/399	LHM[a]
Lactaid	11	9	3	2	3
Lactase N	10	7	5	4	1

[a] Lactose-hydrolysed milk (> 90% lactose-hydrolysed)

Table 4. Milk products (20 g lactose) and lactose maldigestion. Data from Onwulata *et al.* (1989).

Tabla 4. Productos lácteos (20 g de lactosa) y la mala digestión de la lactosa (según datos de Onwulata *et al.*, 1989).

Product	Peak breath H_2 (ppm)	Flatulence[a]
Whole milk (WM)[b]	40	8
Yogurt	2	0
Lactose-hydrolysed milk (LHM)	12	0
Lactaid tablet + WM (756 FCC units/subject)	20	3
Sweet acidophilus milk	41	6

[a] No. of subjects out of 10 reporting symptoms.

[b] Treatments significantly different ($p < 0.05$)

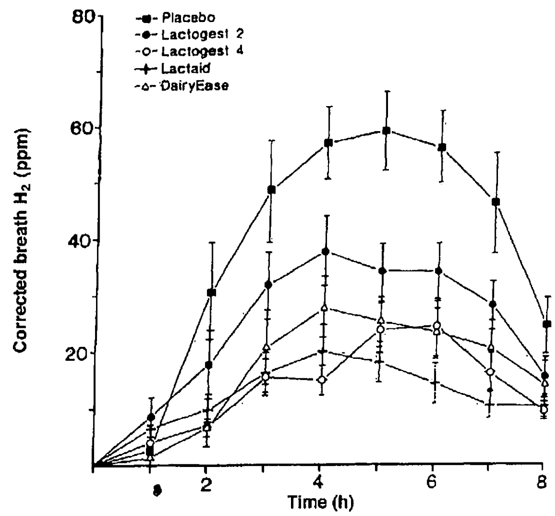

Figure 4. Temporal changes in breath hydrogen excretion in 20 lactose maldigestors in Minnesota after consuming 400 ml of 2% milk together with various lactose digestive aids (6,000 IU of lactase; 3,000 IU as two capsules of Lactogest) (from Lin *et al.*, 1993, with permission).

Figura 4. Variación con el tiempo del hidrógeno eliminado en la respiración con 20 individuos malos digestores de lactosa después de consumir 400 ml de leche al 2% con diferentes aportes de preparados para la digestión de la lactosa (6000 IV de lactasa; 3000 IN en el caso de las dos cápsulas de Lactogest). Datos según Lin *et al.*, 1993.

maximum breath hydrogen concentration after consumption of Lactase N added to 360 ml of milk 5 min before consumption. The digestive efficiency of Lactase N (fungal β-galactosidase) was less than that of Lactaid (yeast β-galactosidase) (Figure 1). Even after consuming a maximum dose of Lactase N, 30% of the subjects reported symptoms of lactose intolerance (Table 3). In another experiment, Rosado *et al.* (1984) observed that 10 of 25 Mexican lactose malabsorbers excreted > 20 ppm of breath hydrogen after consuming 360 ml of milk treated for 5 min with 1 g of Lactaid prior to consumption (Figure 3). From this study it would thus appear that the oral supplements are useful in alleviating lactose intolerance. However, a small population did not respond to the enzyme replacement therapy, which may be due to the lack of sufficient enzymes in the milk. In subsequent studies (Solomons *et al.*, 1985; Barillas and Solomons, 1987; Moskovitz *et al.*, 1987; DiPalma and Collins, 1989; Onwulata *et al.*, 1989) oral supplements of lactase proved to be helpful to various degrees in alleviating lactose maldigestion.

In our laboratory, we compared the efficacy of various milk products including the oral digestive aid, Lactaid, in alleviating lactose maldigestion (Onwulata *et al.*, 1989). Lactaid tablets (756 FCC units), when consumed with whole milk containing 20 g of lactose, reduced the peak breath hydrogen and symptoms significantly in 10 lactose maldigestors (Table 4). However, 30% of the subjects consuming Lactaid still reported flatulence. A more comprehensive study involving comparison of various commercial over-the-counter lactose digestive aids was recently reported by Lin *et al.* (1993). This study was conducted in two locations (Mobile, AL and St. Paul, MN) and compared the efficiency of Lactogest (soft gel

Table 5. Effect of ice cream (18 g of lactose) and lactase (9900 FCC units) consumption on breath hydrogen (ppm) excretion. (Data from Ramírez *et al.*, 1994).

Tabla 5. Efecto de la ingestión de helado (18 g lactosa) y lactasa (9900 FCC unidades) sobre la excreción de hidrógeno respiratorio (según datos de Ramírez *et al.*, 1994).

Test meal	Peak H_2	Cumulative H_2
Ice cream + placebo	30 ± 10	85 ± 32
Ice cream + Lactaid	2 ± 1[a]	4 ± 2[b]
Ice cream + Lactrase	22 ± 6	54 ± 16
Ice cream + Dairy Ease	24 ± 7	61 ± 21

[a] Significantly different from placebo ($p \leq 0.03$)

Table 6. Effect of ice cream (18 g lactose and lactase (9900 FCC units) consumption on gastrointestinal symptoms. Data from Ramírez *et al.* (1994)

Tabla 6. Efecto de la ingestión de helado (18 g de lactosa) y lactasa (9900 FCC unidades) sobre ciertos síntomas gastrointestinales (según los datos de Ramírez *et al.*, 1994).

Test meal	Max. pain	Max. gas
Ice cream + placebo	0.7 ± 0.26	1.2 ± 0.24
Ice cream + Lactaid	0.4 ± 0.22	0.8 ± 0.24
Ice cream + Dairy Ease	0.3 ± 0.15[a]	1.2 ± 0.29
Ice cream + Lactrase	0.2 ± 0.13[a]	0.5 ± 0.22

Symptoms scored: 0 = none; 1 = mild; 2 = moderate; 3 = severe

[a] Significantly different from placebo ($p < 0.05$)

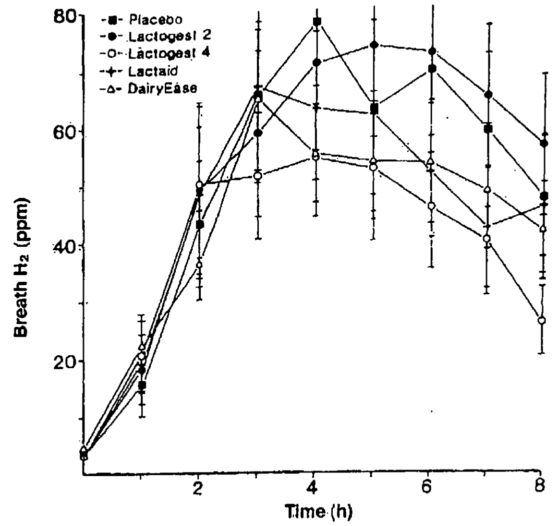

Figure 5. Temporal changes in breath hydrogen excretion in 11 lactose maldigesters in Mobile, Alabama after consuming 50 g of lactose with various lactose digestive aids. See Figure 4 for lactase dose (from Lin *et al.*, 1993, with permission).

Figura 5. Variación con el tiempo del hidrógeno eliminado en la respiración con 11 individuos mal digestores de lactosa después de la ingestión de 50 g de lactosa con varios preparados para la digestión lactosa (datos según Lin *et al.*, 1993). Ver Figura 4 para las dosis de lactasa.

capsules) from Thompson Medical Co., Inc., Lactaid (caplets) from Lactaid, Inc., and Dairy Ease (chewable tablets) from Glenbrook Laboratories, in alleviating lactose maldigestion. All enzyme preparations reduced significantly both peak (Figure 4) and total breath hydrogen secretion when given with milk containing 20 g lactose. In the case of Lactogest, the response was stoichiometric with respect to dose (two capsules vs four capsules). However, both for Lactogest and for Dairy Ease, the peak production of breath hydrogen was > 20 ppm, signifying incomplete lactose digestion. Even for Lactaid, it is evident from standard errors of mean (Figure 4) that a sizeable number of participants excreted more than 20 ppm breath hydrogen. When 50 g of lactose in water was given with 6000 units of any enzyme, the effect on small intestinal lactose digestion was minimal as measured by breath hydrogen concentration (Figure 5). More recently, Ramírez *et al.* (1994) demonstrated differing capabilities of over-the-counter lactase preparations in improving lactose digestion. In this randomized, placebo-controlled trial, 10 healthy lactose intolerant volunteers were challenged with ice cream containing 18 g of lactose together with Lactrase, Dairy Ease or Lactaid (9900 FCC lactase units). Only Lactaid reduced peak breath hydrogen excretion to less than 20 ppm (Table 5), while only Dairy Ease and Lactrase influenced symptoms significantly (Table 6).

From the available data it is evident that oral supplements of lactase are, in general, effective in improving lactose digestion and reducing lactose intolerance symptoms. However, a few individuals do not seem to respond to the exogenous source of enzyme, possibly due to very low levels of endogenous residual lactase. Future research should shed some light on possible subpopulations with very low levels of residual lactase; such subpopulations may need higher levels of exogenous lactase than currently recommended.

Cost of lactase digestive aids

The maximum cost for consuming 240 ml of milk together with the recommended maximum dose of lactase goes up by 100–150% ($0.41–0.59) compared with the cost of consuming milk alone ($0.19–0.23), while the cost of lactose-hydrolysed milk is approximately twice as much as intact milk ($0.36–0.38) (Data from Suárez *et al.*, 1995). Empirical experience shows that prohibitive cost could be one of the reasons why lactose-reduced milk or exogenous lactase supplements are under-used. Cost-reduction research might, therefore, increase the utilization of these aids.

FINAL REMARKS

Exogenous lactase preparations, in general, appear to be effective in improving lactose digestion. Several over-the-counter microbial β-galactosidase preparations are available. The efficacy of these preparations seems to be variable. There are two considerations that may be important in recommending exogenous lactase oral supplements for lactose intolerant individuals: (*i*) there is possibly a subpopulation of lactose maldigesters that either does not respond to or needs a higher dose level of exogenous lactase, and (*ii*) the cost of digestive aids may be a factor in consumer acceptance of these oral supplements.

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