In our study, the beneficial effects of locally applied nitroglycerine on the ease of cannulation were confined to children younger than 1 year, whereas no significant benefit was found in older children. On the other hand, no significant difference in venous status was apparent, even in younger patients. The lack of efficacy of nitroglycerine in group 3 patients indicates local action of this drug rather than systemic effect. Greater ease of cannulation may result from diminished venous reactivity to puncture, induced by the local antispastic vascular action of nitroglycerine.

Nitroglycerine may be more effective in younger children, because they have smaller and more reactive veins than do older patients. These results may also be related to a larger dose per unit of body weight or to thinner skin with more rapid absorption in the younger patients. In any case, the usual ease of venous cannulation in older children reduces the need for nitroglycerine.

We conclude that local application of nitroglycerine ointment is an efficient way of reducing failure in venous cannulation in infants; this technique appears to be simple and innocuous.

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Efficacy of lactase-treated milk for lactose-intolerant pediatric patients

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Lactose malabsorption is a common problem in childhood, and may be associated with eructation or flatus, diarrhea, bloating, and abdominal pain.[1,2] In young children it is often transient, usually following an infectious enteritis; less commonly it is associated with bacterial overgrowth or a primary mucosal abnormality such as celiac disease. Familial absence of lactase is rare, and symptoms appear shortly after the introduction of milk.[3] In older children, lactose malabsorption may result from a genetic "late onset" deficiency of lactase, which has been recognized in the United States more frequently in black children after age 3 years and in white children after age 5 years.[1] Because milk constitutes a major source of carbohydrate and calcium in the diet of children, restriction or elimination of lactose-containing foods poses a potential nutritional risk.

The addition of various β-galactosidases obtained from fungi and yeasts to milk[4,5] has offered an alternative for patients with lactose intolerance. Until recently, such enzyme preparations required 12 to 24 hours incubation for effective hydrolysis of lactose, thereby obviating much of their usefulness away from the home. Recently, Rosado et al.[6] documented in adults the efficacy of adding to milk just prior to ingestion the β-galactosidases derived from the yeast *Kluyveromyces lactis* (LactAid, SugarLo Co., Pleasantville, N.J.). They showed a decrease in both breath hydrogen production (as a manifestation of lactose malabsorption, defined as an increase in hydrogen concentration >20 ppm above baseline) and clinical symptoms after milk ingestion.

We assessed the efficacy of a different β-galactosidase, derived from the fungus *Aspergillus oryzae* (Lactrase, Kremers Urban Company, Milwaukee) on in vivo hydrolysis of lactose in milk in children with lactose intolerance.

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The theoretical advantage of this enzyme over that in LactAid is that it is thought to be stable over a wider range of pH (4.0 to 8.0, with a pH optimum of 4.5 to 5.5), is heat stable, and might therefore be more effective in hydrolyzing lactose just prior to milk ingestion. There are no known side effects of this enzyme.

METHODS

Patients referred to us with symptoms of chronic or recurrent abdominal pain or chronic diarrhea routinely undergo a lactose breath hydrogen test. From January 1985 to June 1986, 106 patients between the ages of 2 and 18 years were documented to have lactose malabsorption; 29 agreed to participate in the study. The study consisted of two parts. In part 1, three capsules of placebo (containing corn syrup solids, maltodextrin, and magnesium stearate) were opened and mixed with whole milk (0.4 oz/kg body weight, maximum 16 oz) within 5 minutes before ingestion. Breath hydrogen samples were obtained every 30 minutes for 5 hours, and analyzed. Only patients with abnormal breath test results were invited to participate in part 2 of the study. In part 2, three capsules (125 mg/capsule) of Lactrase (including above placebo ingredients and active enzyme lactase) were opened and mixed with a similar quantity of whole milk as above within 5 minutes before ingestion. Breath samples were likewise obtained and analyzed. Patients and parents did not know whether the placebo or active enzyme was being used during each test. All patients completed part 2 of the study within 1 week of completion of part 1. Of the 29 patients in part 1 of the study, 16 had abnormal test results, and all agreed to complete part 2. The data obtained from these 16 patients are presented. The study was approved by the Human Investigation Review Committee, New England Medical Center.

Breath hydrogen tests. All patients fasted for a minimum of 8 hours overnight prior to breath hydrogen testing, and had not received antibiotics for a minimum of 2 weeks prior to the examination. Mixed expired air was collected in a 30 mL plastic syringe via nasal prong or mask,[7] and was sealed until analysis for hydrogen concentration was performed (within 3 hours). The standard lactose breath hydrogen test involved ingestion of lactose (Lactol, Jayco Pharmaceuticals, Camp Hill, Pa.), 2 g/kg body weight, to a maximum of 50 g. Breath samples were obtained initially and at 30-minute intervals for 3 hours. An increase in breath hydrogen >10 ppm over fasting level at any of the sample times was indicative of incomplete carbohydrate absorption. The breath test performed after the ingestion of milk with or without placebo was similar to that of the standard lactose breath test, except that breath samples were obtained initially and every 30 minutes for a total of 5 hours.

The exhaled air was analyzed for hydrogen concentration within 3 hours of collection, and expressed as parts per million as determined in a MicroLyzer Model 12 gas chromatograph (Quintron Instruments Company, Milwaukee). This was calibrated with a standard reference gas mixture of 101 ppm hydrogen in nitrogen (M.G. Burdett Scientific Gases, North Branch, N.J.).

The excretion of breath hydrogen was quantified by three methods, each previously shown to provide a sensitive and reproducible index of lactose malabsorption: (1) as the maximum increase in hydrogen concentration above fasting level at any of the 30-minute intervals during the collection[6]; (2) by computing the area under the curve of breath hydrogen concentration by triangulation expressed in units of parts per million per hour[8]; (3) as the summation of the five largest increments of hydrogen concentration over baseline.[9, 10]

Clinical symptom score. A clinical symptom score was generated for each patient. Symptoms of abdominal pain, gas (eructation or flatus), diarrhea (loose watery bowel movements), bloating, nausea, and vomiting within 24 hours of the breath test was recorded. Each of these symptoms was scored as follows: 0, symptoms not present; 1, mild symptoms not interfering with daily activities; 2, moderate to severe symptoms interfering with daily activities. The maximum possible clinical symptom score for any one patient was 10.

Statistical analysis. Standard error of the mean was calculated, and a Student t test was used to test for significant differences between groups.

RESULTS

Sixteen patients aged 3 to 16 years (mean 10.4 years) completed both parts of the study. Symptoms at the time of evaluation were recurrent daily abdominal pain in 10 patients, watery diarrhea in four, and symptoms of excessive gas (eructation or flatus) in two. At the time of evaluation, seven patients were found to have associated constipation, and one patient had ileocolonic Crohn disease. Infectious enteritis was not found in any of the patients. No additional treatment for these associated problems was given between parts 1 and 2 of the study.

Of the 16 patients with abnormal breath test results in part 1 of the study, two patients had no symptoms. In the 14 patients who had symptoms in addition to abnormal breath test results in part 1 of the study, there was a significant decrease in the clinical symptom score (1.64 ± 0.2 vs 0.64 ± 0.3, $P < 0.01$) when active enzyme was added to the milk, compared with addition of placebo. Of the 10 patients with mild symptoms of excess gas (eructation and flatus), six had total resolution of the symptoms; the other four noted no change in symptoms after addition of the enzyme. Two patients who initially had no gaseous symp-

toms developed mild complaints after addition of the active enzyme. Abdominal cramping after part 1 of the study was mild in five patients and severe in two patients; six had total resolution, and one had no change in the mild symptoms. Resolution of the diarrhea occurred when active enzyme was added in both patients who had mild symptoms after part 1. Of the two patients with mild abdominal bloating and distention, one had resolution of the symptom, and one noted no change. Nausea or vomiting was not noted in any of the patients.

There was a significant decrease in the maximum increase in hydrogen production over baseline, the sum of the five highest elevations over baseline and the calculation of the area under the curve after part 2 compared with part 1 of the study (Table). Thus there was evidence of both subjective and objective improvement in clinical symptoms and lactose malabsorption in response to the addition of Lactrase to milk just before ingestion.

Table. Breath hydrogen analysis after parts 1 and 2 of study

	Part 1	Part 2	P
Maximum ΔH_2 (ppm)	47.4 ± 5.4	20.9 ± 6.2	<0.005
Sum of five highest ΔH_2 (ppm)	179.3 ± 24.2	70.3 ± 23.9	<0.005
Area under curve (ppm/h)	126.4 ± 20.9	62.5 ± 15.6	<0.01

Values represent mean ± SE.
ΔH_2, change in breath hydrogen concentration from baseline.

DISCUSSION

The addition of three capsules of Lactrase (375 mg) just before ingestion of whole milk appears to be effective in decreasing both the clinical symptoms and breath hydrogen production in pediatric patients with lactose intolerance. The approximate cost to the patient of this dose of Lactrase is 40¢. We did not determine a response curve to varying doses of the enzyme; therefore, it is possible that a lower dose of the enzyme might be equally as effective. No side effects attributable to the medication were noted, even in the younger patients, who received a proportionately higher dose of the enzyme per kilogram body weight. Two patients did report onset of mild flatulence when the active enzyme was added to milk; this was not present when placebo was used. The enzyme-treated milk was not noted to be distasteful, although several patients reported an increase in sweetness compared with the placebo-treated milk. In this study, using milk as the substrate for the breath test, patients received the equivalent of only 0.6 g lactose/kg body weight. Consequently, those patients with lesser degrees of lactose malabsorption were probably better able to absorb the lower quantity of lactose that the milk provided, and may explain why 13 of the original 29 patients with abnormal standard lactose breath test results (2 g lactose/kg body weight) had a normal value during part 1 of the study.

The hydrogen breath test has been shown to be both sensitive and specific in its ability to quantify incomplete absorption of lactose in milk.[11] We found no correlation between the clinical symptom score or severity of individual symptoms with the magnitude of hydrogen production as measured in the breath test.

Only 50% of adult patients with abnormal lactose breath hydrogen test results have associated symptoms of lactose intolerance, such as diarrhea, bloating, and abdominal pain.[6, 12, 13] Accordingly, enzyme replacement should be considered for use only in patients who have proved symptoms of lactose intolerance, and not solely on the basis of documentation of lactose malabsorption with a lactose breath test. Symptoms of postenteritis lactose intolerance usually resolve within 1 or 2 weeks, and restriction of lactose-containing foods, rather than enzyme replacement, during this time may be sufficient. Some patients with lactose intolerance are able to tolerate yogurt because of the intraintestinal digestion of lactose by the organisms in yogurt.[14] This may be an alternative to enzyme replacement in some patients. A few patients develop symptoms after ingestion of milk despite having normal lactose breath test results.[6] This may in part be caused by milk protein sensitivity rather than by lactose intolerance or difficulty in the collection of breath hydrogen samples. There is no evidence that enzyme replacement is useful for patients sensitive to milk protein.

Previous investigators have demonstrated the ability of in vitro preincubation of milk with exogenous β-galactosidases to decrease hydrogen production and symptoms in lactose-intolerant adults,[6, 15-17] and a decrease in symptoms with in vivo administration of these enzymes.[5] Recently, Barillas and Solomons[18] have shown a decrease in breath hydrogen production when large doses of LactAid were given with milk to lactose-intolerant children in Guatemala. Our study demonstrates that the addition of Lactrase just before the ingestion of milk is effective in decreasing both breath hydrogen production and symptoms in children with lactose intolerance. Further studies are necessary, however, to document the efficacy of this enzyme in relieving symptoms of lactose intolerance after ingestion of other dairy products, such as ice cream or cheese.

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Idiopathic hypereosinophilic syndrome in a 5½-month-old infant

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Hypereosinophilic syndrome is a multisystem disease with peripheral blood eosinophilia of at least 6 months' duration, multiple organ system involvement, and no evidence for other known causes of eosinophilia.[1] It is characteristically a disease of middle-aged men, often has a poor prognosis, and is seldom found during childhood. We report a patient who we believe had HES during infancy.

CASE REPORT

A previously healthy 5½-month-old white boy was taken to his local physician because of a 2-day history of fever (to 38.8° C) and blood-streaked diarrhea. Otitis media was diagnosed, and amoxicillin was given orally. The diarrhea resolved, but the lethargy and fever persisted, and a stiff neck developed 2 days later. The physician, suspecting meningitis, performed lumbar puncture, obtained blood for culture, and prescribed ampicillin and cefotaxime for intravenous administration. The child's initial white blood cell count revealed marked leukocytosis, eosinophilia, and mild thrombocytopenia. He was transferred by ambulance to the Mayo Clinic; en route, generalized tonic-clonic seizures developed, which responded to diazepam given intravenously.

HES	Hypereosinophilic syndrome
CT	Computed tomography
TEC	Total eosinophil count

The patient's mother had had an uncomplicated pregnancy, labor, and delivery. Birth weight was 3960 g, and the patient's medical history was unremarkable. His diet consisted of pasteurized whole cow milk, fruit, and cereals. The family did not eat

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