Clinical and Nutritional Consequences of Lactose Feeding During Persistent Postenteritis Diarrhea

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ABSTRACT. In a double-blind prospective trial, 64 children, 3 to 36 months of age, who had diarrhea for at least 14 days were randomly assigned to receive either a milk-based diet containing 6 g/kg of body weight per day of lactose or the same diet in which the lactose was >95% prehydrolyzed with β-galactosidase. Clinical and nutritional outcomes were compared. The groups were similar at the start of the study. Four of 33 patients (12.1%) in the lactose group were considered to have treatment failure because of excessive purging with or without refusal to accept the diet, compared with 1 of 31 patients (3.2%) in the hydrolyzed lactose group ($P = .20$). Among successfully treated boys, fecal excretion was initially similar, but on days 3 to 5 of the trial the lactose group purged a mean 74.4 g/kg per day (95% confidence limits 17.8, 131.0) compared with 42.0 g/kg per day (95% confidence limits 11.4, 72.6) in the hydrolyzed lactose group ($P < .01$). Diarrhea stopped within 30 hours of hospital admission in 11 children in the hydrolyzed lactose group (35.5%) compared with 1 child in the lactose group (3.3%) ($P < .001$). Fecal excretion of carbohydrate, nitrogen, and energy was significantly greater in the lactose group ($P < .01$), but there were no significant differences in fat excretion or in incremental weight change during hospitalization. Feeding lactose-containing nonhuman milk as the sole nutrient source to children with persistent diarrhea resulted in substantially greater purging which was sufficiently severe to increase the risk of dehydration in these children. *Pediatrics* 1989;84:835–844; *lactose, persistent diarrhea, nutrition, steatorrhea, milk.*

Diarrheal diseases are major causes of morbidity and mortality of infants and young children, particularly in less-developed countries. In addition to the immediate effects of diarrhea on fluid and electrolyte balance, these illnesses also adversely affect children's nutritional status.[1] Diarrheal episodes lasting more than 14 days—so-called persistent diarrheas—have an especially profound negative effect on growth.[2] For this reason, the development of optimal nutritional therapy for persistent diarrhea is an important clinical and public health concern, especially in those countries where both childhood diarrhea and malnutrition are common.

Enteric infections frequently produce incomplete absorption of lactose.[3-6] Unabsorbed carbohydrate contributes to the intraintestinal osmotic load and may thereby increase diarrheal severity. Although elimination of lactose from the diet can alleviate symptoms of intolerance, this may be accomplished at the expense of adequate nutrient intake in settings where children are dependent on milk and affordable alternatives are not available. The clinician is, therefore, faced with a difficult therapeutic dilemma: whether to discontinue milk feedings and risk inadequate nutrient intake or to continue these feedings and possibly induce more severe and prolonged diarrhea and secondary malabsorption. This decision is most difficult at the level of domiciliary or outpatient care when it is often not possible to monitor the outcome of dietary recommendations.

In Lima, Peru, where the present studies were conducted, 1-year-old children from disadvantaged communities receive one third of their energy and one half of their protein from cow's milk.[7] Dilution of this milk or substitution with other available liquids would result in low nutrient consumption. In Peru, as in the populations of many other less-developed countries, lactase activity decreases after

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about 3 years of age and 90% of older children malabsorb lactose.[8] Children from these population groups may be particularly prone to lactose malabsorption following any intestinal insult.

Previous studies of milk feeding during childhood diarrhea are not directly applicable to these issues for several reasons. First, most studies have been conducted either in patients with acute diarrhea or in patients hospitalized for severe persistent diarrhea and its complications. It is not certain whether the results from these earlier studies are relevant to the problem of uncomplicated persistent diarrhea identified in the community. Second, studies of lactose malabsorption based on diagnostic tests of malabsorption do not provide information concerning the likelihood of clinically significant complications, such as secondary dehydration or more prolonged illness. Third, few investigators have considered the effect of lactose malabsorption on the absorption of other nutrients and the overall nutritional consequences of continued lactose feeding. Fourth, many previous investigators have altered the entire diet, not just the lactose content. Thus, it is not possible to distinguish between effects of lactose malabsorption and adverse reactions to other components of the diet. For these reasons, the present studies have been completed to determine the clinical and nutritional consequences of continued feeding with lactose-containing or lactose-hydrolyzed cow's milk in children with persistent diarrhea. The patients studied were identified during community- or clinic-based surveillance to represent children who would normally be managed at home or in outpatient clinics.

PATIENTS AND METHODS

Patients

Children 3 to 36 months of age were recruited from either community surveillance ($n = 60$) or the outpatient clinic of the Instituto de Investigacion Nutricional, Lima ($n = 6$). In both cases, the mother's account of her child's persistent diarrhea was confirmed during sequential observations.

Diarrhea was defined as three or more liquid stools per day, representing a change from normal. The diarrhea had to have persisted for 14 or more days with no more than one intervening diarrhea-free day. Because of our interest in milk feeding as a cause of prolonged illness, children who had received no milk during the diarrheal episode were excluded. Children who were reported to be receiveing more than two breast-feedings per day were also excluded so as not to disrupt their breast-feeding.

All children resided in periurban shanty towns located in the desert surrounding Lima. In these communities, family incomes are derived from poorly paid or unstable employment. Many mothers are employed outside the home, and infants are often cared for by older siblings. Water is delivered by truck and stored in cement tanks or cylinders.[9]

Diarrheal illnesses are common in this population. Children younger than 3 years of age have an average of eight episodes of diarrhea per year. Three percent of these episodes persist more than 14 days resulting in 24 episodes of persistent diarrhea per 100 child-years (C.F. Lanata, personal communication, August 1, 1988).

Sixty-six children completed the study protocol, but 2 children with hepatitis A were later excluded (both from the group of children receiving a diet in which lactose was >95% prehydrolyzed with β-galactosidase) because it was thought that hepatic dysfunction might have contributed to malabsorption. Inclusion of these children would not alter the interpretation of the study.

Diet Fluids

The study diet was designed to simulate the milk prepared for infants in this community, where evaporated milk or full-cream dried milk is reconstituted with water and added sugar or cornstarch.[7] Corn syrup solids were used rather than sucrose to offset the increase in osmolality resulting from hydrolysis of the lactose to glucose and galactose in the hydrolyzed lactose group. The composition of the diet is shown in Table 1. For children in the hydrolyzed lactose group, 30 drops of Lactaid (Lactaid, Inc) were added to each liter of milk, which was left 18 to 24 hours at 4°C to achieve 95% to 99% hydrolysis of the lactose. Periodically, we measured this level of hydrolysis by comparing the postincubation osmolality of the formula with that known to result from complete hydrolysis of the lactose. The diet was offered six times per day (eight times for small babies) up to a maximum of 150 ml/kg per day (110 kcal/kg per day) and was designed to meet all of the child's nutritional requirements. When a feeding was refused or not finished, it was offered again as many as two more times.

Any initial dehydration was corrected using an oral glucose electrolyte solution (90 mmol/L sodium, 20 mmol/L potassium, 30 mmol/L citrate, 20 mmol/L chloride, 2% glucose). The diet was provided at full strength as soon as initial fluid deficits were corrected, usually by 4 hours after admission.

In both dietary groups, diarrheal stool losses and estimated vomiting losses were replaced every 4 hours with an oral solution containing 60 mmol/L of sodium, 20 mmol/L of potassium, 60 mmol/L of chloride, 20 mmol/L of citrate, and 2% glucose. This was given independently of the diet.

TABLE 1. Composition of Study Diets by Food Source*

Ingredients (/150 mL)	Amount (g)	Energy Content	
		kcal	% of total Dietary Energy
Dried whole milk	15.90	78.2	71.0
Fat	4.15	37.4	33.9
Protein	4.21	16.8	15.3
Carbohydrate lactose or glucose/galactose†	6.00	24.0	21.8
Corn syrup solids (glucose polymers)	8.00	32.0	29.0
Total carbohydrate (milk + corn syrup solids)	14.00	56.0	50.8

* 150 mL/kg per body weight per day offered in 6 (or 8) feedings daily.
† 95% hydrolysis of lactose was achieved in one dietary group by addition of Lactaid.

Clinical Procedure

Written informed consent was obtained from parents after the study protocol had been explained to them and they had seen the metabolic ward. The research protocols were approved by the ethics committees of the Instituto de Investigacion Nutricional and the University of Oxford, John Radcliffe Hospital.

Patients were stratified according to age (<6 months, 6 to 18 months, >18 months) and nutritional status (weight for length above or below 2 SD below the 50th percentile using National Center for Health Statistics/Centers for Disease Control [World Health Organization] reference growth tables[10]) and were then randomized to receive one of the two diets. Diets were prepared in the diet kitchen and coded. They were indistinguishable to nursing and clinical study personnel.

When admitted to the hospital, a detailed history was obtained and a physical examination was performed; hydration status was assessed according to a predetermined scheme. Blood was drawn to determine electrolyte, routine hematologic component, total serum protein, and albumin values. Further biochemistry and hematology studies were performed as necessary. Stools were tested for reducing substances, using the method of Kerry and Anderson,[11] both when admitted and thereafter.

Duplicate anthropometric measurements, including supine length, midarm circumference, and skinfold thicknesses at four sites, were taken independently by the same two people on days 1 and 6. Averages of the independent sets of measurements were recorded.

All stool and urine were collected, separately in boys and pooled in girls, during the first 24 hours and again from day 3 to day 5 inclusive. Fecal collections were homogenized with water and analyzed for fat content by the method of Van de Kamer et al[12] and for total energy by adiabatic bomb calorimetry.[13] Fecal and urinary nitrogens were measured using the micromethod of Kjeldahl,[14] and fecal carbohydrate excretion was calculated from the difference between total energy and the sum of fecal nitrogen and fat energy excretions. Percentage of apparent absorption of the individual constituents of the diet was calculated from the difference between the amount consumed and the amount excreted divided by the amount consumed. Apparent nitrogen retention was calculated from the amount consumed minus the total nitrogen lost in feces plus urine divided by the amount consumed. Urine could not be reliably separated from feces in girls, so pooled urine and stool were analyzed. Because fat is not excreted in urine, valid measurements of fat absorption could also be computed for the girls. Energy absorption was calculated for the whole group of patients because the energy contribution of urinary nitrogen is small (<5% in the boys) and, therefore, could be ignored in the girls. However, because of this small error, results of energy absorption have also been calculated for boys only. Nitrogen absorption is presented for boys only, but nitrogen retention is shown for both sexes. Carbohydrate absorption is shown for boys only.

Therapeutic failure was defined as an increase in stool output either to more than 150 g/kg per 24 hours or to more than 100 g/kg per 24 hours together with at least one of the following: vomiting more than 300 mL, refusing more than a third of the diet, severe abdominal distension, or recurrent dehydration of 5% or more (confirmed by weight loss). The study diets were discontinued when children were declared to have therapeutic failure and the stool was collected only to facilitate clinical management.

Three fresh stool samples were collected and examined microscopically for parasites before and after concentration (zinc flotation)[15] and for cryptosporidia by the modified Ziehl-Neelson stain.[16] Two stool samples collected on days 1 and 2 were examined for bacterial pathogens including shigellae, salmonellae, campylobacters, and aeromonas

species. Five colonies of *Escherichia coli* were examined for production of heat-labile and/or heat-stable toxin, verotoxins, and presence of the plasmid (enterocyte adherence factor) coding localized adherence to HEp cells using specific DNA probes at the Division of Enteric Pathogens, Central Public Health Laboratories, London, England. Two stool samples were stored in buffered saline and examined for rotavirus by enzyme-linked immunoassay (Dakopatts plc).

Specific antibiotic therapy was given for microbiologically proven shigellosis. Infections due to *Campylobacter* species and *Giardia lamblia* were treated after completion of the study protocol if diarrhea was still present. Otitis media and proven urinary tract infections were treated as necessary.

Children continued their prescribed diet for 5 days. On the 6th day, the code was broken and those who had received lactose and still had diarrhea received the hydrolyzed lactose diet for one additional day. The hydrolyzed lactose group and the diarrhea-free children from the lactose group received a mixed diet appropriate to their age usually consisting of cereal/vegetable purees and three or four drinks of the hydrolyzed lactose milk. The remaining children in the lactose group received this diet on day 7.

Analysis

Results were compared using Student's *t* tests or analysis of variance for continuous variables and χ^2 or Fisher's exact test for discrete variables. Duration of diarrhea after admission was examined using the log rank test statistic with Kaplan-Meier survival estimates for diet groups.[17] Multivariate analysis was used to examine relationships between fecal excretion of macronutrients and fecal wet weight.

RESULTS

Characteristics of the patients at the time of admission are shown by dietary group in Table 2. Children in the lactose group were slightly better nourished and had diarrhea for fewer days before admission but were more likely to be moderately dehydrated at the time of admission (5% or more dehydration). More patients in the hydrolyzed lactose group had leukocytes in their stool. None of these differences were statistically significant.

Four patients were admitted twice with separate episodes of persistent diarrhea, from 5 to 9 months after the first episode. Three were allocated once to each of the diets and the fourth received the lactose diet on both occasions.

Four children receiving lactose were considered to have dietary failure on days 2 or 3 (Table 3). Of these, two boys augmented their diarrhea to more than 150 g/kg per 24 hours, one girl had increasing stool output estimated at more than 150 g/kg per 24 hours with abdominal distension, vomiting, and

TABLE 2. Characteristics of Patients by Dietary Group When Admitted to Study

	Lactose Diet	Hydrolyzed Lactose Diet
No. of children (boys/girls)	33 (25/8)	31 (19/12)
Age (mo)	18.5 (15.8, 21.2)	18.8 (16.3, 21.3)
Weight (kg)	9.11 (8.36, 9.86)	8.75 (8.13, 9.37)
Nutritional status (*Z* score)		
Weight for age	−1.64 (−1.97, −1.31)	−2.11 (−2.5, −1.72)
Height for age	−1.73 (−2.07, −1.39)	−1.97 (−2.34, −1.6)
Weight for height	−0.75 (−1.06, −0.44)	−1.15 (−1.49, −0.81)
Duration of diarrhea before admission (d)	21.3 (17.9, 24.7)	26.8 (20.8, 32.8)
No. (%) of children vomiting previous 24 h	8 (24.2)	9 (29.0)
No. (%) of children with 6 or more stools in previous 24 h†	18 (54.5)	13 (41.9)
No. (%) of children with leukocytes on stool microscopy	2 (6.1)	5 (16.1)
No. (%) of children dehydrated (5% or more)	5 (15.0)	3 (9.7)
Potential pathogens in stools (1st 2 d)		
Enterotoxigenic *Escherichia coli*	7 (21.2)	6 (19.4)
Campylobacter spp	6 (18.2)	4 (12.9)
Shigella spp	4 (12.1)	4 (12.9)
Salmonella spp	1 (3.0)	3 (9.7)
Aeromonas spp	1 (3.0)	3 (9.7)
Rotavirus	1 (3.0)	1 (3.2)
Cryptosporidium	0 (0.0)	3 (9.7)
Himenolepsis mana	3 (9.1)	2 (6.4)
Strongyloides stercoralis	1 (3.0)	0 (0.0)
Giardia lamblia (in stools and/or duodenal aspirate)	13 (39.4)	12 (38.7)

* Results are expressed as means (95% confidence limits) or number (%). No children had enteropathogenic *E coli* (enterocyte adherence factor probe positive).
† Total number of stools not known in 1 child in each group.

TABLE 3. Details of Treatment Failure*

Diet	Sex	Age (mo)	Duration of Diarrhea at Home (d)	Nutritional Status Z Score			Potential Pathogen on Admission	Day When Failed	Reason for Failure	Stool Pathogen at Time of Failure	Comments
				Wt/Age	Ht/Age	Wt/Ht					
L	M	5.8	15	−1.75	−1.36	−1.05	None	3	Stools >150 g/kg/24 h	None	
L	M	11.6	51	−1.81	−0.82	−1.55	None	2	Stools >150 g/kg/24 h	None	Pyelonephritis, anemia
L	M	16.5	60	−3.65	−3.74	−2.37	*Strongyloides stercoralis*	2	Stools >100 g/kg/24 h, refusal to take fluids or diet, abdominal distension, recurrent dehydration	None	Anemia
L	F	14.1	19	−1.44	−0.26	−1.56	Rotavirus	2	Stools (estimated) >150 g/kg/24 h, vomiting	None	
HL	M	3.8	29	−1.34	−0.79	−1.12	*Aeromonas* spp, *Giardia lamblia*	5	Stools >150 g/kg/24 h	*Shigella* spp	Fever 5th day

* Abbreviations: L, lactose; HL, hydrolyzed lactose; Wt, weight; Ht, height.

weight loss, and one boy had worsening diarrhea, more than 100 g/kg per 24 hours, with abdominal distension, vomiting, and refusal of diet and replacement fluids. One boy in the hydrolyzed lactose group was considered to have treatment failure when diarrhea exceeded 150 g/kg per 24 hours on the 5th day associated with fever. *Shigella flexneri* which had not been identified when he was admitted was isolated from stool on this day. It seems likely that a new infection had developed in this child. The probability of these differences in failure rates occurring by chance is 0.20 (Fisher's exact test) if the single failure in the hydrolyzed lactose group is considered as a "dietary failure" and 0.06 if it is not considered a diet-induced failure.

Reluctance to take the formula was observed occasionally on the first day but did not differ between the groups. The mean percentage of diet accepted during the first 24 hours was 88.5% in the lactose group and 89.2% in the hydrolyzed lactose group. By the third day, 94% of successfully treated children in both groups were accepting all their diet.

More children in the lactose group vomited, but these differences did not reach statistical significance. This difference in vomiting accounts for the slightly higher intakes of nutrients from the diet in the hydrolyzed lactose group (amount offered less vomit and diet refused) (Table 4). When intake from all sources is considered, the lactose group consumed more energy and carbohydrate because their higher fecal outputs required more replacement with glucose electrolyte solution.

The mean fecal outputs of successfully treated boys are shown in Fig 1 for the days when accurate measurements were made. Fecal excretion rates (grams per kilogram of body weight per 24 hours) were initially similar in both diet groups, but during days 3 to 5 children taking lactose had significantly more diarrhea ($P < .01$). The difference in fecal wet weight was due to the higher water content of feces in the lactose group (Table 5). Forty-one percent of the lactose group purged more than 100 g/kg per day while consuming the diet, whereas only one child (5.5%) receiving the hydrolyzed lactose diet had diarrhea of this severity on day 3 only ($P < .02$).

Three children receiving the hydrolyzed lactose diet and one receiving lactose had no further diarrhea following admission. In these cases, either the disease process had run its course or the milk taken at home was causing the persistent diarrhea which ceased with the change in diet. If the results are analyzed with these patients excluded, the mean stool outputs for days 3 to 5 were 74.4 and 45.5 g/kg per day in the lactose and hydrolyzed lactose

TABLE 4. Intakes of Different Nutrients During the Balance Study (Days 3, 4, and 5)*

	Diet	
	Lactose (n = 33)	Hydrolyzed Lactose (n = 31)
Intake from diet		
Energy (kcal/kg/d)	106.07 (103.9, 108.2)	109.16 (108.0, 110.3)
Total carbohydrate (lactose or glucose and galactose and CSS) (g/kg/d)	13.49 (13.24, 13.74)	13.78 (13.63, 13.93)
Fat	4.00 (3.92, 4.08)	4.12 (4.07, 4.17)
Protein	4.06 (3.98, 4.14)	4.18 (4.13, 4.23)
Nitrogen	0.65 (0.64, 0.66)	0.67 (0.66, 0.68)
Intake from all sources (includes replacement fluid)		
Energy (kcal/g/d)	111.74 (109.8, 113.7)	111.37 (110.3, 112.5)
Carbohydrate (g/kg/d)	14.77 (14.39, 15.15)	14.26 (14.07, 14.45)

* Results are mean values with confidence limits in parentheses.

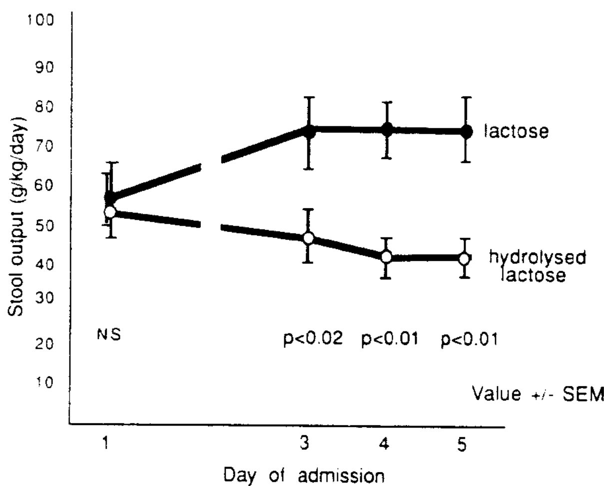

Fig 1. Fecal wet weight by dietary group and day of study for successfully treated boys only.

groups, respectively ($P < .01$, Student's t test) and the interpretation of the study is not changed.

Diarrhea also lasted longer in the hospital in the lactose group. The end of diarrhea was defined as the last liquid stool not followed by another liquid stool within 24 hours. More children in the hydrolyzed lactose group (n = 26, 83.8%) compared with the lactose group (n = 18, 54.5%) had their last liquid stool before the diet was changed on day 6 ($P < .02$). Children with dietary failure are excluded because their diet was changed within the time period. Using a log rank test with Kaplan-Meier estimates to analyze the duration of diarrhea by dietary group (Fig 2), we found that those children consuming lactose had a significantly greater duration of diarrhea ($\chi^2 = 7.9$, 1 *df*, $P = .005$). In this model, the children with dietary failure are included for the period of observation up to the change in diet. This analysis illustrates that the difference in duration of diarrhea is almost entirely due to 11 (35.5%) children in the hydrolyzed lactose group whose diarrhea stopped within 30 hours compared with only 1 child (3.0%) in the lactose group ($P < .001$). Stool testing for reducing substances and pH at the time of admission did not predict these children. Neither duration of diarrhea before admission nor the severity of the diarrhea at home as assessed from the mother's recall was related to the duration of diarrhea or stool output in the hospital.

The net apparent absorption and the coefficients of absorption for the selected constituents of the diet are shown in Table 5. The lactose group absorbed less carbohydrate, but, nevertheless, absorption was more than 80% of intake. Carbohydrate excretion was correlated with fecal output in the lactose group ($r = .59$, $P < .01$) but not in the hydrolyzed lactose group ($r = .24$) (Fig 3). All of the children had steatorrhea (fecal fat excretion of more than 15% of intake) and 78% of children excreted more than 20% of intake. Coefficients of fat absorption were not significantly different between the two groups. Fat excretion was positively correlated with fecal wet weight ($r = .57$, $P \leq .01$). This correlation was highly significant in the lactose group ($r = .71$, $P < .01$) but did not reach significance at the .05 level in the hydrolyzed lactose group ($r = .37$) (Fig 4). Fecal nitrogen excretion was significantly correlated with fecal wet weight in both groups (lactose, $r = .60$; hydrolyzed lactose, $r = .88$; $P < .01$ for both). Nitrogen absorption and energy absorption were significantly lower in the lactose group compared with the hydrolyzed lactose group (Table 5). The diet provided a generous level of dietary protein, and all children were in apparent positive nitrogen balance with no differences in net nitrogen retention between the groups.

Weight gain was similar in the two groups, and there were no changes in length or in skinfold thickness measurements.

TABLE 5. Stool Composition and Absorption of Nutrients in the Two Dietary Groups (Days 3, 4, and 5)*

	Lactose Diet	Hydrolyzed Lactose Diet	Significance ($P<$)
Fecal wet weight (g/d)	669.2 (96.5, 1241.9) [22]	386.2 (56.1, 716.3) [18]	.001
Fecal dry weight (g/d)	31.77 (7.67, 55.77) [22]	32.54 (0.00, 65.54) [18]	NS
Fecal water content (%)	94.44 (89.54, 99.34) [22]	90.72 (82.72, 98.72) [18]	.001
Apparent nutrient absorption			
* Fat (g/kg/d)†	2.75 (2.59, 2.91) [29]	2.94 (2.83, 3.05) [30]	NS
+ Carbohydrate (g/kg/d)‡	12.09 (11.66, 12.52) [22]	13.28 (12.99, 13.57) [18]	.01
+ Nitrogen (g/kg/d)‡	0.52 (0.49, 0.55) [22]	0.56 (0.55, 0.57) [18]	.01
Energy (kcal/kg/d)			
Boys and girls	89.56 (87.32, 91.80) [29]	95.68 (94.18, 97.18) [30]	.01
Boys only	90.34 (87.72, 92.96) [22]	95.49 (93.42, 97.56) [18]	.01
Coefficient of absorption			
Fat†	0.69 (0.65, 0.73) [29]	0.72 (0.69, 0.75) [30]	NS
Carbohydrate‡	0.90 (0.88, 0.92) [22]	0.97 (0.96, 0.98) [18]	.01
Nitrogen‡	0.78 (0.75, 0.81) [22]	0.83 (0.82, 0.84) [18]	.01
Energy			
Boys and girls	0.80 (0.78, 0.82) [29]	0.86 (0.85, 0.87) [30]	.01
Boys only	0.80 (0.77, 0.83) [22]	0.85 (0.84, 0.86) [18]	.01
* Coefficient of nitrogen retention	0.34 (0.29, 0.39) [29]	0.34 (0.30, 0.38) [30]	NS

* Results are means with confidence limits in parentheses and numbers of patients in brackets. Only dietary successes included.
† Boys and girls.
‡ Boys only.

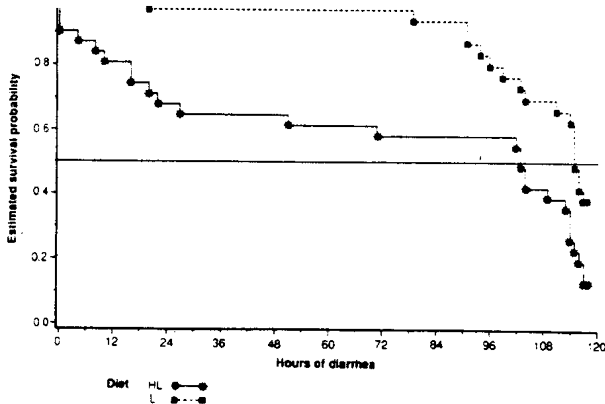

Fig 2. Probability of continuing diarrhea by dietary group based on Kaplan-Meier estimates. Abbreviations: L, lactose; HL, hydrolyzed lactose.

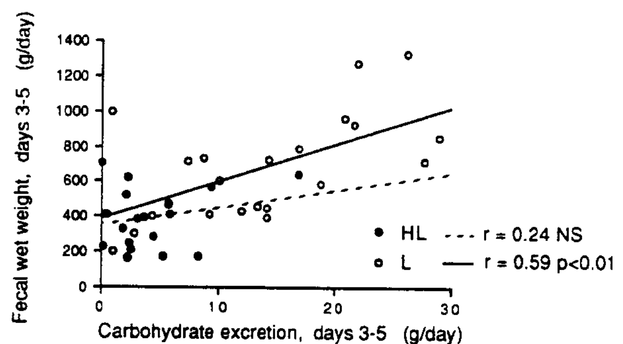

Fig 3. Correlation of fecal wet weight with fecal carbohydrate excretion, days 3 to 5, by dietary group. Abbreviations: L, lactose; HL, hydrolyzed lactose.

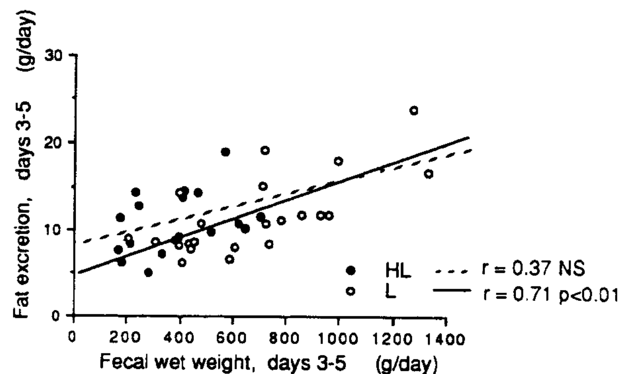

Fig 4. Correlation of fecal fat excretion with fecal wet weight, days 3 to 5, by dietary group. Abbreviations: L, lactose; HL, hydrolyzed lactose.

DISCUSSION

We have demonstrated a significantly better outcome in the hospital for children with persistent diarrhea fed hydrolyzed lactose milk compared with similar children given milk containing 6 g/kg per day of lactose. Except for the difference in lactose content, the only difference between the two diets in this study was the osmolality. Hydrolysis of lactose to glucose and galactose increased the osmolality of the hydrolyzed lactose diet from approximately 350 mOsmol/kg of diet to about 450 mOsmol/kg. A higher osmolality would be expected to exacerbate rather than improve diarrhea and would have tended to mask differences between the groups attributable to lactose malabsorption.

Nearly all (92%) of the infants studied were under surveillance in the community before admission. Children were offered admission to the study protocol if they had had diarrhea for 14 days. Se-

verity of the diarrhea and evidence of malabsorption (fecal reducing substances) were not used as inclusion criteria. All of the children were less than 10% dehydrated when admitted, and only one was severely malnourished (weight for height >3 SD below the National Center of Health Statistics' mean). Given the limitations of hospital services available for this community, these children would normally have been managed at home. Thus, we have extended the earlier observations that lactose intolerance is common in infants with severe persistent diarrhea[18-21] to encompass unselected children with persistent diarrhea in the community.

The greater duration and severity of diarrhea in the infants consuming lactose were clinically important. Fecal excretion rates of greater than 100 g/kg per day, which were reached by more than one third of children receiving lactose, could lead to severe dehydration if losses were not adequately replaced. These children also had a tendency to vomit more, which would have also contributed to the risk of severe dehydration. The excess diarrhea attributable to lactose intolerance in our study is in keeping with the doubling of stool output reported by Mann et al[22] in seven babies hospitalized for severe persistent diarrhea who were given lactose milk compared with two other groups of babies given lactose-free soy formula or low-lactose milk.

The reduced median duration of diarrhea in the hydrolyzed lactose group in the present study can be explained by the subgroup of children who ceased having diarrhea soon after starting the hydrolyzed lactose diet. Thus, it appears that approximately one third of these patients who were drinking nonhuman milks before admission had persistent illness caused exclusively by lactose malabsorption. Apparently, other causal mechanisms were operative in the remaining children in the hydrolyzed lactose group, although it is possible that they also had some degree of lactose malabsorption contributing to their persistent diarrhea before admission. In other words, it can be concluded that a subgroup of patients with persistent diarrhea may have lactose malabsorption as the only causal mechanism for prolonged illness, but even more patients may have clinically important lactose malabsorption.

In addition to the differences in clinical outcome, we also found significant differences in absorption of carbohydrates, nitrogen, and energy between the two groups. The children in the hydrolyzed lactose group absorbed an average 6 kcal/kg per day more energy than those in the lactose group. This difference is small and in the context of this study did not result in detectable differences in weight gain between the groups. However, by dint of frequently offered feedings, we were able to achieve reasonable caloric intakes in nearly all children and these intakes were sufficient to counteract the increased fecal energy losses. The lactose group absorbed an average calorie excess of 15.8 kcal/kg per day and the hydrolyzed lactose group 22.4 kcal/kg per day more than their calculated maintenance energy requirements.[23] This does not take into account increased energy requirements because of illness or the additional energy needed for "catch-up" growth. By contrast, diets at home may be only marginally adequate, and mothers often do not have time to offer frequent feedings to their infants. Small differences in energy absorption as observed in the lactose group may become critical when dietary intake is barely adequate to cover maintenance requirements.

An additional disadvantage of lactose in the diet would be the increased losses of other nutrients induced by lactose malabsorption. Our results indicate that greater losses of nitrogen and energy accompanied the increased fecal carbohydrate losses. In several previous studies, the effect of lactose malabsorption on the absorption of nitrogen was examined. Three-day stool collections from four healthy adults with, and two without, lactose malabsorption identified by breath hydrogen testing revealed no difference in absorption of nitrogen from milks with different lactose content.[24] However, only two of the "lactose malabsorbers" increased stool output and diarrhea developed in none. Graham and Paige[25] found increases in stool water and nitrogen excretion following change to a lactose-containing diet (8 g of lactose per kilogram of body weight per day) in four lactose-intolerant children who had recovered from malnutrition. A negative correlation between nitrogen absorption and stool weight was found in the study by Mann et al[22] in South Africa. Despite the fact that these latter babies seem to have had more severe intestinal damage with lower coefficients of absorption of fat and nitrogen, our findings are in general agreement with these results.

In only a few studies was the effect of lactose malabsorption on fat absorption assessed. Calloway and Chenoweth[24] found no effect of lactose ingestion by known lactose malabsorbers on their fat excretion. Debongnie et al[26] studied ileal effluent in adults with and without lactase deficiency, comparing consumption of hydrolyzed lactose with lactose-milk. Recovery of fat from the ileum was not related to lactose malabsorption. On the other hand, Graham and Paige[25] documented an increase in fat excretion following introduction of a lactose-containing diet in their patients. The South African investigators[22] found a negative correlation between apparent fat absorption and stool output. They did

not correlate fat absorption and carbohydrate absorption, but review of their results does not reveal an apparent difference between the median fat absorption for the different dietary groups. In our patients receiving lactose, fecal fat excretion was significantly positively correlated with stool output, but there was no correlation between fecal fat excretion and fecal carbohydrate excretion ($r = .14$). There was no significant difference in apparent fat absorption between the two dietary groups. In addition, there was significant ($F = 17.8$, $P < .005$) improvement in the fit of a linear regression of fecal wet weight on fecal carbohydrate excretion ($r = .60$) following addition of fecal fat excretion as a second independent variable ($r = .79$). It appears that lactose absorption and fat absorption are independent. Either a third independent factor is associated both with increasing severity of diarrhea and fat malabsorption or steatorrhea per se exacerbates diarrhea. This question can only be resolved by further studies in which children are randomly assigned to diets differing only in fat content.

Many studies have now shown that, using appropriate diets, it is beneficial to continue feeding during acute diarrhea.[27-34] We have demonstrated that nutritional intakes sufficient to prevent weight faltering can be achieved by oral feeding in children with postenteritis persistent diarrhea. However, a diet containing 6 g/kg per day of lactose offered as the sole nutrient source resulted in potentially dangerous purging rates and increased fecal losses of nitrogen, energy, and carbohydrate. Therefore, lactose consumption should be reduced or eliminated in the diet of children with persistent diarrhea, even those with uncomplicated persistent diarrhea identified in the community.

It may not be necessary to remove lactose completely from the diet. Lactose malabsorption is dose related,[35] and there is evidence that merely reducing lactose ingestion is sufficient to eliminate symptoms. Isolauri[36] used a lactose-containing milk as part of a mixed diet in weaned infants, and Chandrasekaran et al[37] found that 74 of 90 lactose-intolerant infants improved when given curd (a fermented milk product containing 2.5 to 3.0 g of lactose per 100 g). Dewit et al[38] found that ingestion of yogurt resulted in less carbohydrate malabsorption as assessed by the breath hydrogen test in Algerian boys with chronic diarrhea. Ultimately, the promotion of inexpensive, locally available diets developed in the light of experimental findings will provide the best chance of improving nutrition during persistent diarrhea and halting the progression to malnutrition. We have clarified the deleterious effects of lactose, but, clearly, other factors are also important. Modification of the fat content of the diet is likely to have the greatest impact on energy losses in the feces.

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REFERENCES

1. Brown KH, MacLean WC Jr. Nutritional management of acute diarrhea: an appraisal of the alternatives. *Pediatrics.* 1984;73:119–125
2. Black RE, Brown KH, Becker S. Effects of diarrhea associated with specific enteropathogens on the growth of children in rural Bangladesh. *Pediatrics.* 1984;73:799–805
3. Kumar V, Chandrasekaran R, Bhaskar R. Carbohydrate intolerance associated with acute gastroenteritis. *Clin Pediatr.* 1977;16:1123–1127
4. Davidson GP, Goodwin D, Robb TA. Incidence and duration of lactose malabsorption in children hospitalised with acute enteritis: study in a well-nourished urban population. *J Pediatr.* 1984;105:587–590
5. Hyams JS, Kraus PJ, Gleason PA. Lactose malabsorption following rotavirus infection in young children. *J Pediatr.* 1981;89:916–918
6. Brown KH, Black RE, Parry L. The effect of acute diarrhea on lactose malabsorption among Bangladeshi children. *Am J Clin Nutr.* 1980;33:2226–2227
7. Brown KH, Black RE, Lopez de Romaña G, Kanashiro HC. Infant feeding practices and their relationship with diarrheal and other diseases in Huascar, Peru. *Pediatrics.* 1989;83:31–40
8. Paige DM, Leonardo E, Cordano A, Nakashima J, Adrianzen TB, Graham GG. Lactose intolerance in Peruvian children: effect of age and early nutrition. *Am J Clin Nutr.* 1972;25:297–301
9. Lopez de Romaña G, Brown KH, Black RE. Health and growth of infants and young children in Huascar, Peru. *Ecol Food Nutr.* 1987;19:213–219
10. *NCHS Growth Curves for Children, Birth–18 Years, United States.* Rockville, MD: National Center for Health Statistics, Vital and Health Statistics series 11, No. 165 (DHEW publication PHS 78–1650), 1977
11. Kerry KR, Anderson CM. A ward test for sugar in faeces. *Lancet.* 1964;1:981–982
12. Van de Kamer JH, Huinink H, Weyers A. Estimation of fat in feces, food and other biological materials. *J Biol Chem.* 1949;177:347–355
13. Raymond WF, Canaway FJ, Harris CE. An adiabetic bomb calorimeter. *J Sci Instrum.* 1957;24:501–503
14. Horowitz W. *Official Methods of Analysis of the Association of Official Analytical Chemists.* 12th ed. Washington, DC: Association of Official Analytical Chemists; 1975
15. Smith JW, Bartlett MS. Diagnostic parasitology: introduction and methods. In Lennnette EH, ed. *Manual of Clinical Microbiology.* 4th ed. Washington, DC: American Society for Microbiology; 1985:600
16. Henricksen SA, Pohlenz JFL. Staining of Cryptosporidia by

a modified Ziehl-Neelsen technique. *Acta Vet Scand.* 1981;22:594–596
17. Lee ET. *Statistical Methods and Survival Data Analysis.* Belmont, CA: Lifetime Learning Publications; 1980:105–121
18. Burke V, Kerry KR, Anderson CM. The relationship of dietary lactose to refractory diarrhoea in infancy. *Aust Paediatr J.* 1965;1:147–159
19. Arora NK, Bhan MK, Ghai OP. Protracted diarrhoea of infancy. *Indian Paediatr.* 1981;18:373–378
20. Munir M. Protracted diarrhoea in infants and young children: a clinical evaluation with special reference to the role of infection. *Paediatr Indones.* 1982;22:98
21. Coello-Ramirez P, Medina-Huerta LA, Diaz-Bensussen S, Zuniga V, Larrosa-Haro A. Etiologia de la diarrea prolongada en ninos. *Bol Med Hosp Infant Mex.* 1984;41:605–610
22. Mann MD, Hill ID, Peat GM, Bowie MD. Protein and fat absorption in prolonged diarrhoea in infancy. *Arch Dis Child.* 1982;57:268–273
23. Food and Agriculture Organization/World Health Organization. *Energy and Protein Requirements.* Geneva, Switzerland: WHO Technical Report Series No. 724; 1985
24. Calloway DH, Chenoweth WL. Utilization of nutrients in milk- and wheat-based by men with adequate and reduced abilities to absorb lactose, 1: energy and nitrogen. *Am J Clin Nutr.* 1973;26:939–951
25. Graham GG, Paige DM. Nutritional implications of low intestinal lactase activity. In: *Intestinal Enzyme Deficiencies and Their Nutritional Implications.* Stockholm, Sweden: Ulmquist & Wiksell; 1973:45–51. Symposia of the Swedish Nutritional Foundation XI
26. Debongnie JC, Newcomer AD, McGill DB, Phillips SF. Absorption of nutrients in lactase deficiency. *Dig Dis Sci.* 1979;24:225–231
27. Gabr M, Maraghi S, Morsi S. Management of lactose intolerance secondary to acute diarrhea with a soy-based, lactose-free formula. *Clin Ther.* 1979;2:271–276
28. Ransome OJ, Roode H. Early introduction of milk feeds in acute infantile gastro-enteritis. *S Afr Med J.* 1984;65:127–128
29. Plaszek M, Walker-Smith JA. Comparison of two feeding regimens following acute gastroenteritis in infancy. *J Pediatr Gastroenterol Nutr.* 1984;3:245–248
30. Deleted in proof
31. Soenarto Y, Suprapto, Sutrisno DS, Sebodo T, Radjlman Lahmuddin. Milk lactose: the amount tolerated in post diarrhoeal children. *Trop Pediatr Environ Child Health.* 1979;25:104–106
32. Chung AW, Viscorova B. The effect of early oral feeding versus early oral starvation on the course of infantile diarrhoea. *J Pediatr.* 1948;33:14–22
33. Mitchell JE, Donald WD, Birdsong M. A review of 396 cases of acute diarrhoea in which early oral feedings were employed in treatment. *J Pediatr.* 1949;35:529–539
34. Brown KH, Gastafladuy AS, Saavedra JM, et al. Effect of continued oral feeding on clinical and nutritional outcomes of acute diarrhea in children. *J Pediatr.* 1988;112:191–200
35. Barillas C, Solomons NW. Effective reduction of lactose maldigestion in preschool children by direct addition of β-galactosidases to milk at mealtime. *Pediatrics.* 1987;79:766–772
36. Isolauri E, Vesikari T, Saha P, Viander M. Milk versus no milk in rapid refeeding after acute gastroenteritis. *J Pediatr Gastroenterol Nutr.* 1986;5:254–261
37. Chandrasekaran R, Kumar V, Walia BNS, Moorthy B. Carbohydrate intolerance in infants with acute diarrhoea and its complications. *Acta Paediatr Scand.* 1975;64:483–488
38. Dewit O, Boudraa G, Touhami M, Desjeux JF. Breath hydrogen test and stool characteristics after ingestion of milk and yoghurt in malnourished children with chronic diarrhoea and lactase deficiency. *J Trop Pediatr.* 1987;33:177–180

WORKING DURING PREGNANCY

Nearly two million working women give birth each year, and studies show that a growing number of them are working later into their pregnancies, sometimes up to first contraction. . .The National Center for Health Statistics detected a. . .trend in unpublished and recently analyzed 1982 data it collected from 2000 working women 15 to 44 years old. . .Thirty-five percent were still on the job in the ninth month of pregnancy, nearly twice the 19 percent reported in a similar study in 1973. Eleven percent worked right up to birth.

Submitted by Student

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