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A trial of lactase in the management of infant colic

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Objective: To investigate transient lactose intolerance as a factor in the aetiology of infant colic.
Design: We undertook a randomized, double-blind, crossover trial of lactase and placebo drops added to milk formula to determine whether this method of reducing lactose intake affected infant colic.
Subjects: Infants with colic were referred from clinics in keeping with Wessel's modified criteria.
Interventions: Infants were randomly allocated to add either lactase or placebo drops to their formula feeds for 1 week, followed by 2 days 'wash out'. The addition was changed for the second week so that subjects served as their own control. The formulas were kept refrigerated for 24 h before ingestion. The parents kept a diary of their baby's crying time.
Results: Thirteen babies completed the trial, of whom nine were boys. The mean birth weight was 3.7 kg (8.2 lb). Colic symptoms began in less than 1 month in 12 of the babies. The effect of the lactase was to reduce crying time by 1.14 h per day (CI 0.23–2.05). The reduction in crying time was significant ($t = 2.75$, d.f. = 11, $P = 0.019$).
Conclusion: Transient lactose intolerance may have a role in the aetiology of infant colic. Lactase drops require prior incubation with milk formula to be effective. The response to lactase in this study supports 'colic', i.e. spasm of the large intestine as a factor in these infants' discomfort.

Key words: formula feeds, infant colic, lactase, lactose intolerance.

Introduction

The cause of infant colic remains in dispute, but some authors favour excessive production of colonic gas as an important aetiological factor (Miller & Barr, 1991). The clinical observations of abdominal distension with paroxysmal crying relieved by passing flatus support this theory (Illingworth, 1985). Transient lactose intolerance is the most likely cause of excessive colonic gas (Barr *et al.*, 1984). Incomplete lactose absorption by the small intestine provides a carbohydrate substrate for colonic bacteria; the bacteria metabolize lactose with the production of hydrogen (Levitt, 1969). Lactose intolerance has been studied in babies with primary excessive crying using stool pH and clinitest (Liebman, 1981), and hydrogen breath test (Moore *et al.*, 1988; Hyams *et al.*, 1989), but the results of these studies have been conflicting (Treem, 1994). We had anecdotal evidence that infant colic tends to settle in babies whose milk formula has been incubated with lactase (Lactaid, Clonmel Health Care, Co. Tipperary). We undertook a double-blind, cross-over trial of lactase and placebo drops added to milk

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formula to determine whether this method of reducing lactose intake affected infant colic.

Methods

We recruited infants from general practitioners and paediatric clinics whose history was compatible with colic and who were otherwise well. We used Wessel's criteria (Wessel *et al.*, 1954) for infant colic, except we did not require a 3-week duration of symptoms. Babies were included in the trial if they had full force crying for 3 or more hours a day, for 3 or more days a week. Parental consent was obtained after full explanation of the purpose and nature of the trial. β-galactosidase (lactase) has been commercially produced from the yeast *Kluyveromyces lactis* and is available as *Lactaid*, an over-the-counter preparation. We obtained both *Lactaid* and placebo preparations from the manufacturers. The study was approved by the hospital ethics committee.

Infants were allocated the preparations in the order (A) lactase first then placebo or (B) placebo first then lactase; using random permuted blocks of size four to ensure that the numbers of babies assigned to the two treatment orders were fairly even. In a block of size four, two babies were allocated to the order A and two to the order B. There are six permutations of a block of size four (AABB, BBAA, ABAB, BABA, BAAB and ABBA) and these six groupings were randomized. The resulting sequence was the method used to assign the preparation order to babies in the study. The preparations were given in bottles which were marked 'week 1' and 'week 2' to ensure the double-blind nature of the trial. Mothers were instructed to add three drops of lactase or placebo to each feed and refrigerate for 24 h before feeding it to the baby. Lactase or placebo was added to the formula for 1 week followed by 2 days 'wash-out'. The treatment was swapped in the second week so that each subject served as his or her control.

All the babies were examined clinically before the study to exclude any other cause of upset. The parent was asked to keep a diary containing information on their baby's crying time, stool habit and details of the volume, strength and type of formula. The babies were weighed at the start and finish of the trial, and the stools were checked for reducing substances using clinitest tablets (Ames Division, Dublin).

Standard descriptive statistics were used to summarize the information recorded. The analysis of crying time was based on a model for a two-period crossover trial with a covariate (Jones & Kenward, 1989).

Results

Thirteen babies completed the trial, of whom nine were boys. The babies ranged in age from 23 to 112 days (mean 53.5 days, s.d. 26.2) at entry to the trial. The mean birthweight was 3.7 kg (8.2 lb) with a range of 2.9–4.7 kg (6.3–10.3 lb). All babies remained on the formula chosen by the parent, with four on Cow & Gate (Cow & Gate Ireland Ltd, Dublin), four on Millumil (Milupa, Dublin), four on S.M.A. (S.M.A. Nutrition, Dublin) and one on Ostermilk (H. J. Heinz Co. Ltd, Middlesex). Colic symptoms began at less than 1 month of age in 12 babies, and at 6 weeks in one baby. Symptoms started at less than 1 week of age in three babies. Eleven of the 13 babies had their stools checked with clinitest for reducing substances. Two babies showed a trace to one-quarter per cent positive and the remainder were negative. There was no difference in stool clinitest whether on lactaid or placebo.

Crying time

Seven babies received treatment in the order Lactaid first followed by placebo (the LP group), the reverse order applied to the remaining six babies (the PL group). Crying time per day was calculated for the first period and for the second period.

The LP group and the PL group were compared in an analysis of covariance with 'total crying time over the two periods' as the dependent variable and age as the covariate. The covariate age was not significant ($F_{1,10}=3.00$, $P=0.114$). The group effect was also not significant ($F_{1,10}=0.82$, $P=0.387$) implying no evidence of a treatment by period interaction.

The LP group and the PL group were then compared in an analysis of covariance with 'difference in crying time over the two periods (period 1 minus period 2)' as the dependent

Table 1. Mean crying time (h/day) of babies receiving Lactaid or placebo

	Placebo ($n=6$)	Lactaid ($n=7$)	Difference
Mean (s.e.)	2.57	1.43	1.14 (0.413)

variable and age as the covariate. The covariate age was not significant ($F_{1,10}=0.02$, $P=0.886$). The group effect was significant ($F_{1,10}=5.67$, $P=0.038$). The effect of Lactaid (without taking age into account) was to reduce crying time by 1.14 h per day (95% C.I. 0.23–2.05), Table 1.

Discussion

Miller *et al.* (1990), reported that lactase drops had no significant effect on the duration of crying in breast-fed infants, when the lactase was given directly into the babies' mouths during a breast feed. Hydrogen excretion was not reduced in the treated group in Miller's study, suggesting that the lactase had been inactivated in the stomach. In contrast Medow *et al.* (1990), have shown that lactase tablets are effective in older children with lactose intolerance, when given with food. Lactase tablets significantly reduced clinical symptoms and hydrogen breath excretion after a lactose load. Lactase drops are sourced from yeast and act best at neutral pH, whereas lactase tablets are derived from *Aspergillus* and have an optimum pH of 4.4 (Rosado *et al.*, 1984). Our results show that lactase drops added to milk formula 24 h prior to feeding resulted in a significant reduction in crying time in babies with infant colic. Lactase drops may require prior incubation with milk to be effective in infant colic. A previous double-blind crossover study of lactase (Stahlberg & Savilahti, 1986) showed no difference in crying time between four milks with and without lactase. The babies were older than the babies in the present study of classical early infant colic. The lack of response maybe explained by their older age, because it is known that there is little correlation between first quarter colic and the crying of late infancy (James-Roberts, 1991).

The symptoms of colic suggest that transient lactose intolerance is a possible aetiological factor, but studies of carbohydrate absorbtion in babies with infant colic have not been consistent. Liebman (1981), found no association between babies with colic and lactose intolerance as measured by stool pH and reducing substances. Breath hydrogen testing is a more sensitive indicator of incomplete lactose absorbtion in the small intestine (Levitt, 1969). This method has shown increased hydrogen excretion in infants with colic compared with controls (Moore *et al.*, 1988). Barr *et al.* (1984) have shown that there is a spectrum of increased breath hydrogen in normal babies, and that hydrogen excretion has a similar monthly timing pattern to that of infant colic. A mild functional lactase insufficiency as suggested by Barr *et al.* (1984) may explain the crying pattern of early infancy. Their suggestion is in keeping with the results of this study, showing that milk formula pretreated with lactase will reduce crying time in infant colic. Hyams *et al.* (1989) found no significant difference in breath hydrogen excretion and transit time between babies with colic and controls after a standard dose of lactulose. This latter report does not examine lactose intolerance, but does provide evidence that intestinal motility and bacterial metabolism of lactulose in the colon are similar in babies with colic and controls. Barr *et al.* (1984) also reported interesting 24-h studies in which hydrogen excretion was inversely related to the state of arousal. They observed in addition dramatic decreases in hydrogen after a bowel movement. These individual studies seem to conflict with the known correlation between hydrogen excretion and infant colic. However, the sequence suggests that hydrogen excretion builds up when a baby is quiet, eventually stimulating peristalsis and defecation, which in some babies causes colic. Treem (1994) pointed out that the symptoms of colic are in keeping with gas production as a cause, including the evening peak of symptoms due to accumulation of malabsorbed carbohydrate after a day's feeding.

Crying behaviour may be improved by changing milk formulas to either casein hydrolysate or soya bean formulas (Forsyth,

1991). These formulas have a reduced lactose content. Many of the trials reporting that a change in protein content has an effect on colic were not controlled for an associated reduction in lactose (Campbell, 1989; Lothe & Lindberg, 1989). The difficulties in evaluating changing formulas are often aggravated by changes in both protein and carbohydrate content. This study has the advantage that there was no change in infant formulas. The only variable was the presence of added lactase or placebo to the milk. The observed reduction in crying time can only be explained by the effect of lactase on the milk formula. The study by Malone *et al.* (1995) have shown that lactase is effective *in vitro* when used in circumstances similiar to this study.

Dicyclomine hydrochloride has been shown to improve colic in controlled trials (Illingworth, 1958; Hwang & Danielsson, 1985). The effect of the drug supports the suggestion that the gut is the source of the baby's upset, because dicyclomine is an enteral antispasmodic. The response to lactase in this study supports transient lactose intolerance as an important factor in these babies' discomforts. The findings vindicate the term 'colic' in these babies, because abdominal discomfort in transient lactose intolerance is likely to be mediated by spasm of the large intestine.

James-Roberts (1991) reviewed persistent crying during infancy in different communities. The pattern was similar in different communities and nearly one-third of babies show prolonged crying at 6–8 weeks. Less than one in 10 babies have persistent crying after 3 months of age. It is unlikely that persistent crying after 3 months of age is caused by lactose intolerance, because breath hydrogen excretion is not excessive after the first quarter and there is little overlap between first-quarter crying and later first-year crying (James-Roberts, 1991). Other factors, such as milk allergy and maturation of the gastrointestinal tract, may play a role. Other conditions may mimic colic; one baby referred for this study was not included because the baby was found to have infantile spasms.

Barr *et al.* (1992) carefully described crying patterns in early infancy. This study distinguished a Wessel subgroup of babies with colic separate from the normal crying of early infancy. We suggest that the Wessel subgroup are babies prone to colonic hyperperistalsis, which can be stimulated by gaseous distension. A hypersensitive colon could be stimulated by other upsets, but hydrogen breath tests suggest that gaseous distention is the most important trigger in the first few months of life. This trial shows that lactase-treated formulas reduce early infant colic. A similar trial with the added information provided by hydrogen breath testing would be of value.

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