Journal of Human Nutrition and Dietetics

The Official Journal of The British Dietetic Association

Volume 14 • Issue 5 • October 2001 • ISSN 0952-3871
Edited by Annie Anderson

Improvement of symptoms in infant colic following reduction of lactose load with lactase

D. Kanabar, M. Randhawa & P. Clayton

pp 359-363

Blackwell Science

www.blackwell-science.com/jhn

Improvement of symptoms in infant colic following reduction of lactose load with lactase

D. Kanabar,* M. Randhawa* and P. Clayton†

*Department of Paediatrics, Guy's Hospital, London, UK; †Crosscare Ltd, Dublin, Ireland

Correspondence
P. Clayton,
Crosscare Ltd,
Dublin,
Ireland
E-mail: paul@adrenalin.co.uk

Keywords
breath hydrogen, hypolactasia, infant colic, lactose intolerance.

Accepted
June 2001

Abstract

Transient lactose intolerance has been identified as a possible causative factor in infant colic. A double-blind randomised placebo-controlled crossover study to investigate this has been undertaken in 53 babies with symptoms of colic. Pre-incubation of the feed with lactase resulted in breath hydrogen levels and total crying time which were both at least 45% lower than figures with placebo treatment, in 26% of the full trial group (95% confidence interval 12.9% to 44.4%), and in 38% of compliers (95% confidence interval 18.8% to 59.4%). The remainder did not respond to the same extent. These findings suggest that infant colic may have a multiple aetiology, and that in a significant number of cases the immediate cause is transient lactose intolerance, in which cases pretreatment of feeds with lactase can result in considerable symptomatic benefits.

Introduction

Infant colic affects between 10% and 30% of babies between 3 and 13 weeks (James-Roberts, 1991; Weisbult, 1994), whether breast- or formula-fed (Adams & Davidson, 1987; Thomas *et al.*, 1987). Although it is not generally considered to be a serious medical condition, colic can lead to failure to thrive and in extreme cases to dehydration and electrolyte imbalance. More commonly, it may contribute to impaired parent–child bonding, and increase the risk of child abuse (Sumpter, 1987). The aetiology of the condition is unclear, and this has led to a proliferation of treatment strategies, none of which is very successful. Indeed, one of the most commonly used remedies (dimethicone) was shown to be no better than placebo in two double-blind cross-over studies (Metcalf *et al.*, 1994; Danielson & Hwang, 1996).

One current theory suggests that colic may be caused by transient relative lactase deficiency, which may reflect an immature digestive system (Levitt, 1969; Barr *et al.*, 1984; Miller *et al.*, 1990). The resulting failure to break down all the lactose in the feed allows significant amounts of lactose in breast milk or formula to enter the large bowel. It then becomes a substrate for lactobacilli and bifidobacteria in the colon, which break it down in a fermentation reaction to produce lactic acid and hydrogen. The subsequent increase in breath hydrogen is an accepted indirect biomarker for hypolactasia (Levitt, 1969), and has been reported in infants with colic (Moore *et al.*, 1988; Miller *et al.*, 1989; Barr, 1990) The rapid production of hydrogen in the lower bowel distends the colon, causing pain. The osmotic pressures generated by the lactose and lactic acid in the colon cause an influx of water, leading to further distension and acidic diarrhoea.

This model of colic implies that symptoms could be relieved by reducing the lactose content of the infant's feed. This hypothesis has already

been tested in a small double-blind study in which the feed of colicky babies was pre-incubated with lactase (Kearney *et al.*, 1998). The results were positive, but the trial size ($n = 13$) precluded formal proof.

We set up a larger, double-blind, placebo-controlled study with randomised entry and cross-over. Infants who met the trial criteria were assessed in both limbs of the study for colic symptoms and breath hydrogen.

Experimental procedures

Subjects

Fifty-three infants aged between 3 and 13 weeks were recruited. New mothers were given trial-related literature in the recovery rooms, and our interest in colicky babies was explained to them. First phase follow-up was a phone call from our trial midwife to all mothers on our list, reminding them that we wanted to hear from them if their babies developed the symptoms of colic. During the following weeks, mothers whose babies developed colic and who called in to report this went into our second phase follow-up. Follow-up was by the midwife who visited the parents in their homes, and determined acceptability according to the trial criteria. These included full-force crying in excess of 3 h per day, for 3 days or more per week, together with spasm, lower limb flexure and diarrhoea, as described by Wessel *et al.* (1954), except that a slightly shorter (14-day) duration of symptoms was accepted. Parental consent was obtained after full explanation of the purpose and nature of the trial, and the study was approved by the Guy's & St Thomas Ethics Committee.

Experimental design

The trial design was that of a randomised double-blind two-period crossover study. Subjects were randomly assigned by use of a predetermined computer-generated randomization schedule to the verum or placebo arm for an initial period of 10 days, and then switched after a 5-day wash-out phase, during which neither active nor placebo was used, to 10 days in the alternate arm. The severity of symptoms of colic was assessed by the parents, who filled in a daily record denoting total crying time per treatment and washout period, and feed details throughout the entire study. Breath hydrogen testing was done before and after one feed, during the last 2 days at the end of each arm (Fig. 1).

The preparations were given in bottles marked with the infant's entry code, and either 'A' or 'B', to maintain the double-blind. All bottles were retrieved at the end of both courses in order to ascertain compliance. Bottles initially contained 7 mL of either active or placebo; infants were designated non-compliant if either return exceeded 3.5 mL.

Lactase incubation

In formula-fed babies, mothers were instructed to add two drops of lactase or placebo to each (cooled or body temperature) feed, shake gently, refrigerate for approximately 4 h before re-warming and giving as normal. A similar procedure has been shown to be effective in increasing milk osmolality *in vitro* (Malone *et al.*, 1995).

In breast-fed babies, mothers were instructed to express the fore-milk (which has the highest lactose content) into a tea-spoon or other sterile container, and add to this four drops of the lactase

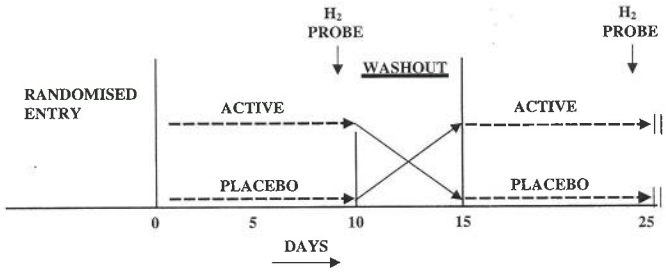

Figure 1 Experimental design.

or placebo. They then breast-fed as usual, and gave the treated fore-milk to the infant at the end of the feed. Standard enzyme kinetics predict that the relatively short incubation period would be at least partially compensated for by the higher concentration of lactase in the small volume of expressed fore-milk. This is supported by an *in vitro* analysis in which we showed that four drops of lactase enzyme added to 15-mL samples of Aptamil achieved 50–70% conversion of lactose within 5 min; and by the fact that this method of using lactase has been used successfully in Eire (M. Buckley, personal communication). Some lactase activity may have continued in the stomach after feeding, as the relatively high gastric pH in infants would not immediately denature the enzyme, but this was not quantifiable. The intention of both methods was to reduce the lactose load, rather than eliminate it entirely.

Materials

Beta-galactosidase (lactase) is commercially produced from *Aspergillus*, and is available as a bacteriologically sterile over-the-counter preparation. Lactase and a heat-inactivated placebo were obtained from the manufacturers. Appearance and packaging of active and placebo were identical.

Breath hydrogen measurement

Breath hydrogen was measured using a Micro H2 (Micro Medical Ltd, Chatham, UK). This is a portable hydrogen monitor designed for the simple screening of lactose or sucrose malabsorption by automatic sensor drift detection (Peuhkuri *et al.*, 1998). Samples were taken using face-masks with one-way valves, before feeding, and at 10-min intervals thereafter, up to a maximum of 120 min or until breath hydrogen returned to the prefeed baseline value. All readings over baseline were summed to give an approximate AUC value.

Statistical methods

Since data for both cry-time and breath hydrogen levels had very non-normal distributions, even after transformation, distribution-independent summary statistics and analytical methods were utilized. Group responses have been summarized in terms of medians and interquartile ranges. Analysis of data from the two-period crossover study was undertaken using the non-parametric method described by Koch (1972), to examine the effects of treatment, period and order of the treatments. Exact binomial confidence intervals of proportions of 'responders' (per '*a priori*' definition) have been determined. Analyses were undertaken using SAS® release 8.1 software. All hypothesis tests were two-tailed, with the threshold for significance taken as $P = 0.05$.

Results

Of the 53 babies who entered the trial, 46 subjects were available for cry time analysis, and breath hydrogen data were available in 34 subjects. The reasons for non-availability included changes of address, and a failure to understand the dosage instructions. A significant proportion of the babies for whom data were available (14/46) were found to be non-compliant (Table 1). This is in contrast to the general practice experience in Ireland, where lactase has been used for 5 years, and where

Table 1 Lactase enzyme research results

	Active (median)	Placebo (median)	% Reduction	*P*
Intention to treat (n = 46)				
Breath hydrogen	6.0 p.p.m.	11.5 p.p.m.	50.0%	< 0.0001
Cry time	657.5 min	847.5 min	22.4%	= 0.09
Compliant (n = 32)				
Breath hydrogen	6.0 p.p.m.	9.5 p.p.m.	36.8%	= 0.0007
Cry time	520.0 min	872.5 min	40.4%	= 0.0052

compliance is high (C. Maguire, personal communication). It was subsequently noted that the study group contained a high incidence of non-native English speakers; a multilingual pack insert is now under consideration.

In this context, an 'intention to treat' analysis (undertaken in all babies for whom some data were available) showed that lactase pretreatment of feeds was associated with a markedly and statistically significant lower breath hydrogen than was the case with placebo pretreatment (medians – 6.0 p.p.m. with active, 11.5 p.p.m. with placebo, $P < 0.0001$). It also tended to be associated with lower cry time (medians – active 657.5 min, placebo 847.5 min) but this difference did not quite reach significance ($P = 0.09$). However, a 'per protocol' analysis excluding those babies considered non-compliant revealed that, in the compliers, cry time was significantly lower in the active group than in the placebo group (median cry time 520 min and 872.5 min, respectively, $P = 0.0052$). Median breath hydrogen was also significantly lower (medians – active 6.0 p.p.m., placebo 9.5 p.p.m., $P = 0.0007$).

Critically, in light of the natural course of colic, the active-placebo differences in cry time were not significantly affected by whether lactase was given before or after placebo ($P = 0.98$ for cry time in compliers analysis). In addition, there was no significant difference ($P = 0.32$ for cry time in compliers analysis) between cry time and breath hydrogen in the first and second treatment periods.

The predetermined criteria for treatment success (> 45% reduction in cry time and breath hydrogen) were achieved by 26% of babies overall (95% confidence interval 12.9–44.4%), and by 38% of compliers (95% confidence interval 18.8–59.4%). Results were not appreciably different when subgroups of babies who were exclusively bottle fed, or fed by both bottle and breast, were considered, but there were insufficient exclusively breast-fed babies to permit any consideration of that subgroup.

Discussion

Lactose intolerance is a suspected cause of infant colic. In one study, crying time was halved by changing from milk-based formula to soy-based formula with a zero lactose content (Campbell, 1989). More recently, low lactose formulas have been marketed, which might be expected to be similarly effective.

At least one study (Miller *et al.*, 1990) did not show a significant effect with lactase given to breast-fed babies. This study's case definitions did not include duration measurements. Potentially more seriously, the lactase was given orally after feeding, a strategy which would have made dosage difficult and greatly reduced the chances of the lactase acting preventatively. A more recent report found that pre-incubation of formula with lactase was effective in cases of infant colic (Kearney *et al.*, 1998).

However, although lactose intolerance is probably a cause of colic, it is probably not the only cause of colic; an earlier study found no correlation between colic and lactose intolerance as measured by stool pH and reducing substances (Liebman, 1981). Furthermore, studies which measured breath hydrogen in infants with colic produced inconsistent results (Barr *et al.*, 1984; Moore *et al.*, 1988; Hyams *et al.*, 1989).

In our study, only a subset of subjects responded to lactase, but in the group that did respond, cry time and/or breath hydrogen were significantly reduced. In light of the above reports, we interpret our results as follows.

The diagnostic entity of infant colic does not describe aetiology, but is merely a description of symptoms. In these situations, it is not unusual to find that new analytical techniques may reveal that the condition is heterogeneous, with different underlying patho-aetiologies. We believe that this is what the trial shows; and that the difference between responders and non-responders is due to different aetiologies.

In infants whose colic is due to lactose intolerance, the application of lactase would be expected to lead to symptomatic improvement. In infants whose colic is caused by other factors such as early allergy to bovine serum albumen (BSA), low-level infection, metabolic errors, etc., lactase could have no effect.

In this context, lactase becomes a diagnostic agent. Where it works, lactose intolerance can be assumed to be the cause of the infant's symptoms,

and lactase can logically be recommended for use for a period of around 3 months. In infants who do not benefit, a negative result with lactase indicates a different aetiology and may form the basis for further investigation and different treatment decisions. This model lends itself to a simple treatment algorithm for infant colic as follows:

Treat infant with lactase. If positive response, continue for as long as the symptoms of colic persist. If negative, switch to low-allergenicity feed. If positive response to low-allergen feed, continue low-allergen feed until weaning. If negative, further investigation may be required, i.e. screen for low-level infection, metabolic error, possible child abuse, etc. Our study was designed to screen the efficacy of lactose load reduction in infant colic at the primary health care level. The trial findings are unlikely to apply to infants referred to paediatric gastroenterology units, where alternative aetiologies may predominate.

An algorithm such as this may reduce the numbers of parents presenting at surgery, A & E departments, etc., and may conceivably help to reduce the numbers of infants proceeding to established BSA and other allergies.

Finally, making additions to a feed and then incubating could theoretically increase the risk of microbial contamination. However, the clear instructions for use with lactase (i.e. incubate in a fridge, then warm before feeding) minimize the potential risk.

In conclusion, we found that pre-incubation of feed with lactase was associated with a significant active/placebo difference in both cry time and breath hydrogen in those who used lactase as indicated.

Acknowledgment

This study was funded by Crosscare Ltd, Dublin.

References

Adams, L.M. & Davidson, M. (1987) Present concepts of infant colic. *Paed. Ann.* **16**, 817–820.

Barr, R.G. (1990) The normal crying curve – what do we really know. *Dev. Med. Child Neurol.* **32**, 368–372.

Barr, R.G., Kinsnorth Patterson, D. & Woodreidge, J. (1984) Breath hydrogen excretion in normal newborn infants. Evidence for functional lactase beyond the first month of life. *J. Pediatr.* **104**, 527–533.

Campbell, J.P. (1989) Dietary treatment of infant colic: a double blind study. *J. R. Coll. Pract.* **39**, 11–14.

Danielson, B. & Hwang, C.D. (1996) Treatment of infant colic with surface active substance (simethicone). *Acta Paeditr. Scand.* 74, 446–450.

Hyams, J.S., Geertsma, M.A., Etienne, N.L. & Treem, W.R. (1989) Colonic hydrogen production in infants with colic. *J. Pediatr.* **115**, 592–594.

James-Roberts, I.S. (1991) Persistent infant crying. *Arch. Dis Child.* **66**, 53–55.

Kearney, P.J., Malone, A.J., Hayes, T., Cole, M. & Hyland, M. (1998) A trial of lactase in the management of infant colic. *J. Hum. Nutr. Dietet.* **11**, 281–285.

Koch, G.G. (1972) The use of non-parametric methods in the statistical analysis of the two-period change-over design. *Biometrics* **28**, 577–584.

Levitt, M.D. (1969) Production and excretion of hydrogen gas in man. *New. Eng. J. Med.* **281**, 122–127.

Liebman, W.M. (1981) Infantile colic: Association with lactose and milk intolerance. *J. Am. Med. Assoc.* **245**, 732–733.

Malone, A.J., Kearney, P.J. & Dugga, P.F. (1995) The effect of a lactase on the osmolality of an infant formula. *Irish J. Med. Sci.* **164**, 22.

Metcalf, T.J., Irono, T.G., Sher, L.D. & Young, P.C. (1994) Simethicone in the treatment of infant colic: a randomised placebo-controlled trial. *Paediatrics* **94**, 29–34.

Miller, A.R. & Barr, R.G. (1991) Infantile colic: is it a gut issue? *Pediatr. Clin. North Am.* **38**, 1407–1423.

Miller, J.J., McVeagh, P., Fleet, G.H. & Brant, J.C. (1989) Breath hydrogen excretion in infants with colic. *Arch. Dis. Child* **64**, 725–729.

Miller, J.J., McVeagh, P., Fleet, G.H., Petocz, P. & Brand, J.C. (1990) Effect of yeast lactase enzyme on 'colic' in infants fed human milk. *J. Pediatr.* **117**, 261–263.

Moore, D.J., Robb, T.A. & Davidson, G.P. (1988) Breath hydrogen response to milk containing lactose in colicky and non-colicky infants. *J. Pediatr.* **113**, 979–984.

Peuhkuri, K., Poussa, T. & Korpela, R. (1998) Comparison of a portable breath hydrogen analyser (Micro H2) with a Quinton MicroLyzer in measuring lactose maldigestion, and the evaluation of a Micro H2 for diagnosing hypolactasia. *Scand. J. Clin. Lab. Invest.* **58**, 217–224.

Sumpter, E.A. (1987) In *Primary Pediatric Care.* eds R. A. Hoekelman, S. Blatman, S. B. Friedman, pp. 714–715. Mosky.

Thomas, D.W., McSilliga, K., Eisenberg, L.D., Lieberman, H.M. & Rissman, E.M. (1987) Infantile colic and type of milk feeding. *Am. J. Dis Child* **141**, 451–453.

Weisbult, H. (1994) In *Pediatric Therapy*, 14th edn. eds F. D. Burg, E. R. Wald, *et al.* pp. 233–236. Philadelphia: Saunders.

Wessel, M.A., Cobb, J.C., Jackson, E.B., Harris, G.S. & Detwiler, A.C. (1954) Paroxysmal fussing in infancy, sometimes called 'colic'. *Pediatrics* **14**, 421–424.