Human milk in the management of protracted diarrhoea of infancy

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SUMMARY Eleven of 13 children with the protracted diarrhoea syndrome of infancy were successfully treated with human milk. All the infants, who were severely malnourished, had deteriorated while fed on a wide range of highly modified formulas. Seven infants responded promptly with cessation of weight loss and diarrhoea; in four others, human milk was used to re-establish oral nutrition after a period of intravenous nutrition when all other measures had failed. Two children did not respond to human milk. Despite its high lactose content, human milk has nutritional and immunological properties that may reverse many of the factors thought to cause the protracted diarrhoea syndrome, and we conclude that it has an important role in management of this syndrome and may obviate the need for intravenous nutrition as a life saving measure.

Protracted diarrhoea syndrome of infancy, which may occur during the first year of life, is an unusual but life threatening illness that presents a diagnostic and therapeutic challenge. Persistent diarrhoea refractory to standard treatment results in severe malnutrition. The differential diagnosis has been reviewed elsewhere.¹⁻⁴ Malnutrition requires urgent empirical treatment while investigations are being undertaken and specific diagnosis, if made at all, is usually retrospective. The associated malnutrition may produce secondary factors which aggravate the diarrhoea. The uncertain pathogenesis of the diarrhoea and its secondary effects^{2,3,5} have resulted in a variety of treatments being recommended, including disaccharide or carbohydrate free formulas, milks based on protein other than cows' milk protein,³ elemental or predigested formulas,^{6,7} broad spectrum oral antibiotics,^{3,8} cholestyramine,⁸ antisecretory agents,⁹ corticosteroids,^{2,3} oral disodium chromoglycate, colostomy,²⁻⁴ and administration of lactobacilli.^{2,4} As none of these measures have been consistently successful, even when tried in combination, prolonged intravenous nutrition is frequently necessary.

Although high in lactose, human milk has many characteristics that may be beneficial to these infants. We report our experience using donor human milk in the management of patients with this syndrome.

Patients and methods

The patients were referred to this hospital during the five year period 1978-83. Those infants who had undergone surgery or had intestinal anatomical anomalies were excluded, as were those with cystic fibrosis or coeliac disease. Investigations were individually selected but followed broadly the scheme outlined by other workers.¹⁻³ Eleven patients who met the criteria for diagnosing severe protracted diarrhoea and who were successfully treated with human milk, were reviewed retrospectively. During this period, two other children did not respond to human milk and required prolonged intravenous nutrition. Human milk, which was supplied by the hospital's breast milk bank, was used fresh or after pasteurisation by the Holder method (63°C for 30 minutes in a Scott-Western model SW70 Automatic Human Milk Pasteurizer). All infants had received therapeutic trials in hospital of various modified formulas before being given human milk. The mean age of presentation with diarrhoea was 2 months (range 7 days to 4 months), and diarrhoea had been present for between one and 14 months (mean 3.5 months) before human milk was tried. Referral to this unit was frequently made because of an anticipated need for intravenous nutrition. There were 7 boys and four girls. One child (case 5) was the product of a consanguineous marriage. The relevant clinical data is shown in Tables 1 and 2.

Table 1 Details of 11 children with protracted diarrhoea syndrome of infancy who were successfully treated with human milk

Case no	Age at onset of diarrhoea	Duration of diarrhoea before human milk feeding (mths)	Stool pathogen	IgE/RAST	Jejunal biopsy	Oral feeds tried			Pregestimil	Chicken based	Amino acid based	Intravenous nutrition	Duration on human milk (mths)	Comments and other treatment
						Lactose free	Soya based	lactose free						
1	11 wks	1.5	Rotavirus	N	ND	F	NT	NT	F	NT	NT	Considered	3	Cows' milk challenge reaction at 5 mths
2	1 wk	5	—	N	N	F	F	F	F	NT	NT	—	1	—
3	16 wks	4	—	N	N	F	F	F	NT	NT	NT	—	4	Recurrent wheezing
4	6 wks	1	Echo 23 virus	N	ND	F	F	F	F	NT	NT	Considered	2	—
5	9 dys	14	—	Cows' milk, rice	PVA	F	F	F	F	F	NT	Twice	1.5 1	Steroids, metronidazole, loperamide, oral cromoglycate, IVN dependent before human milk
6	16 wks	2	<i>Escherichia coli</i>	N	ND	F	F	F	F	NT	NT	Considered	1	Oral gentamycin
7	6 wks	3	<i>salmonella</i>	Cows' milk, soya, fish, egg	N	F	F	F	F	F	F	Twice	5 2	Allergic rashes, anaphylaxis to soya
8	6 wks	1.5	Rotavirus	N	ND	F	F	F	NT	F	NT	Considered	1.5	—
9	9 wks	1	Adenovirus	N	ND	F	NT	F	F	F	NT	Considered	3	Recurrent anaemia
10	13 wks	2	Echo 3 virus	Cows' milk	N	F	F	F	F	F	NT	Twice	3 2	Oral cromoglycate, loperamide, anaphylaxis to chicken and chicken and Pregestimil
11	21 wks	4	—	Cows' milk soya	PVA	F	F	F	NT	NT	F	Three times	6	Oral cromoglycate, scurvy recurrent anaemia

N=normal; ND=Not done; F=failed; NT=not tried; PVA=Partial villous atrophy; RAST=radioallergosorbent test.

Table 2 Weight before starting human milk in 11 children with protracted diarrhoea syndrome of infancy

Case no	Weight (kg)	Standard deviation score
1	4.1	-3.7
2	5.15	-2.4
3	6.6	-2.8
4	3.4	-3.0
5*	7.8	-3.0
6	4.2	-3.9
7	3.65	-3.9
8	3.6	-4.0
9	3.45	-3.8
10*	4.6	-1.9
11	4.9	-4.1

* Oedematous. Patients 5, 6, and 10 are Asian, the remainder Caucasian.

Six infants had an infective agent (five viral, one bacterial) isolated from their stools at the onset of diarrhoea. Two patients had more than one pathogen present. Serum immunoglobulins were

normal in most instances. One patient (case 2) had transient IgA deficiency, and IgE radioallergosorbent testing (Pharmacia Diagnostics) provided serological evidence of cows' milk protein sensitivity in four infants. Three had evidence of sensitivity to more than one food substance. Jejunal biopsy was performed in 6 infants and showed partial villus atrophy in two.

Stool sugar chromatography confirmed disaccharide or monosaccharide intolerance, or both in all infants at some stage in their illness. Other drug treatments given concurrently are outlined in Table 1.

Results

The mean duration of diarrhoea until introduction of human milk was 3.5 months (range 1 month to 14 months), during which time a variety of dietary and

Figure (a) and (b) Patient in case 7 showing malnutrition at presentation (a) and four months after starting human milk (b). (He has an 'allergic' skin rash).

other treatments had been attempted. In all instances, diarrhoea resolved and weight loss stopped within 7 days of introducing human milk feeds.

Infants were considered to have 'failed' on a modified formula if there was no reduction in stool volume and frequency, and no cessation of weight loss. The usual sequence of formula changes was glucose/saline→lactose free milk→soya based lactose free milk→Pregestimil (Mead Johnson)→Comminuted Chicken Meat Formula (Cow and Gate)→Vivonex (Eaton Laboratories) or another elemental amino acid/peptide based formula. Details of the formula changes for each infant are included in Table 1.

Continued weight loss was expected while the infant was receiving glucose/saline or a dilute formula containing inadequate calories. All children failed to improve on a lactose free formula. All 9 children tried on regimens including soya based formula and all 8 tried on feeds including Pregestimil, failed to improve. Five infants (cases 1, 2, 3, 4, and 6) were then fed donor human milk. In three patients (cases 1, 4, and 6) this was considered a final attempt at oral nutrition before instituting total parenteral nutrition, because of their advanced state of malnutrition. In all five patients there was an impressive improvement in stool consistency, reduced stool frequency, cessation of weight loss, and modest weight gain within 7 days of receiving human milk. A further two children (cases 8 and 9) had received and failed to improve on diets including chicken based formula.³ Human milk produced similar success in these, obviating the need for parenteral nutrition.

The remaining four children (cases 5, 7, 10, and 11) required total intravenous nutrition during their illness. None had received human milk before their first course of intravenous nutrition. In these infants the indication for total intravenous nutrition was failure to respond to a wide variety of formulas including comminuted chicken meat (cases 5 and 10) and an amino acid based formula (Vivonex or Albumaid, Scientific Hospital Supplies) (cases 7 and 11). In these four children human milk was used as the first oral feed after a period of total bowel rest and was successful in all cases in achieving oral nutrition and serving as a basis for subsequent introduction of other foods. All four patients required more than one period of intravenous nutrition because of subsequent relapse caused by intercurrent enteric infection or an allergic enteric reaction to other food substances. Reintroduction of human milk at the end of a period of total intravenous nutrition was always accepted. The Figure shows the patient in case 7 before and after treatment.

Eight children are now on normal diets and have normal growth at a mean follow up age of 2.3 years (range 6 months to 5 years). Three (cases 5, 10, and 11) are still on various restricted diets—in the first, growth remains static, but the second is growing normally, and the third child is showing catch up growth.

Discussion

The management of infants with protracted diarrhoea syndrome is complex and demanding. By necessity, our report of treatment using human milk is uncontrolled. We have been impressed by the ability of human milk to reverse consistently the cycle of diarrhoea and malnutrition where other treatments have failed. Sunshine¹⁰ outlined some of the benefits of human milk in the management of short gut syndrome and non-specific enterocolitis. In 7 of our patients, children who had failed on a wide variety of recommended specialised formulas, human milk succeeded in avoiding the need for intravenous nutrition. In another four it enabled the re-establishment of oral nutrition after a period of intravenous nutrition following failure to improve during trials of various formulas. All of our patients had shown evidence of either monosaccharide or disaccharide intolerance at some stage before receiving human milk but, paradoxically, the high lactose content of human milk was well tolerated. Human milk was introduced gradually over two to three days, during which time stool consistency improved as full strength milk was taken. Older infants who seemed to dislike the taste of the donor human milk accepted it when sweetened with saccharine. Tube feeding or intravenous fluid support was occasionally required. Stools became more acidic after human milk and contained oligosaccharides when analysed by stool chromatography. This is a normal finding,¹¹ not to be misinterpreted as indicating carbohydrate intolerance.

As the sole caloric source, human milk, and especially banked human milk, which is extremely variable in its caloric content, may not be adequate for catch up growth. Analysis of this hospital's banked human milk showed, on average, a caloric content of 51.3 kcal/100 ml with wide variability (range 34.5 to 63.1 kcal/100 ml) (L Smith in preparation). Having achieved initial control and modest weight gain on human milk, some infants received human milk supplemented with medium chain triglyceride oil and glucose polymer powder to achieve catch up growth before introducing other foods.

The mechanisms thought to be responsible for perpetuating the cycle of diarrhoea, malabsorption,

and malnutrition are multiple and complex.¹⁻³ It has been suggested that an initial enteric infection in a susceptible individual may cause functional or structural intestinal mucosal damage that may result in absorption of food protein macromolecules, subsequent sensitisation, and an allergic enteropathy. Bacterial contamination of the upper small bowel with anaerobes, *Escherichia coli*, and other bacteria seems to be common in this syndrome,⁵ and increased adhesion of *E coli* to mucosal cells has recently been shown.²⁸ Bacterial contamination is associated with monosaccharide malabsorption,¹² probably mediated by the action of deconjugated bile acids whose products are capable of inducing mucosal damage and inhibiting mucosal ($\text{Na}^+ - \text{K}^+$) adenosine triphosphatase activity.²⁹ Unabsorbed carbohydrates have a further osmotic diarrhoeal effect. Malnutrition ensues, and may itself cause mucosal damage¹³ and pancreatic insufficiency.¹⁴ These mechanisms were not investigated in detail in our patients, and the relative importance of each in the pathogenesis of severe protracted diarrhoea syndrome has not been established.

The importance of food protein sensitivity in this condition has been emphasised by others.¹⁻⁴ It is of note that 6 children in our series had an identified enteric infection at the start of their illness and four had radioallergosorbent test evidence of food sensitivity, though many more showed clinical evidence of this. One child had transient IgA deficiency that may have been a predisposing factor to antigen absorption. Although normal jejunal histology was found in most biopsies (4 of 6) it is recognised that histological lesions may be patchy or absent in this syndrome.^{15 16}

Human milk has many desirable properties which are not present in modified formulas and which may be of benefit in reversing some of these mechanisms. In contrast to elemental feeds, human milk is of low osmolality and hence does not exacerbate or precipitate osmotic diarrhoea.

The importance of food protein sensitivity in the perpetuation of this condition has already been emphasised. Human milk is hypoallergic, is rich in secretory IgA, which confers passive mucosal protection against antigens and bacterial organisms,¹⁷ and also contains substances that may hasten 'gut closure'.^{18 19}

Human milk contains a complex array of humoral and cellular elements that have potent immunological and anti-infective properties against bacteria known to contaminate the upper small bowel of these children.^{20 21} These elements include lactoferrin; transferrin; lactoperoxidase; immunoglobulins A, G, and M; lysozymes; complement; T and B lymphocytes; and macrophages.²⁰ In particular,

secretory IgA play an important role in preventing bacterial adhesion to small bowel mucosal cells.²¹

Absorption of human milk lipid is more efficient than that of cows' milk because of its fatty acid composition and because of the presence of inherent lipolytic activity.²² Furthermore, iron, calcium, and zinc are better absorbed.²²

Human milk contains a recently recognised heat stable growth promoting factor²³ that may encourage repair of damaged intestinal mucosa. Finally, banked human milk is readily available to most children's hospitals within reach of a maternity/neonatal unit and is much cheaper than elemental or modified formulas.

In the treatment of protracted diarrhoea syndrome in infancy there are a number of conceivable disadvantages of human milk. The high lactose load might be considered deleterious for a condition known to be associated with secondary lactose intolerance. This, however, did not emerge as a problem in our patients, although some infants showed evidence of continuing carbohydrate intolerance after human milk had been stopped. It may be possible to pretreat human milk with exogenous lactase,²⁴ but this has not been investigated extensively and in our experience has not been necessary.

It is known that maternally ingested food protein may be excreted in breast milk and it is possible that antigens may be allergenic to the gut of these infants.²⁵

Freezing and pasteurising human milk removes some of its beneficial qualities.^{20 26} Cellular elements are largely destroyed²⁷ or adhere to glass, but IgA, lysozymes, vitamin binding capacity, *Lactobacillus bifidus* growth factor, and antiviral properties are largely retained. Until the relative importance of each factor has been investigated it would seem safer to recommend that infants with severe protracted diarrhoea syndrome should be fed fresh human milk provided it can be shown to be bacteriologically safe.

In spite of these theoretical disadvantages, practical experience suggests they are not clinically significant.

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