Personal practice

Sugar intolerance complicating acute gastroenteritis

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SUMMARY Sugar intolerance occurred in 31 of 200 children admitted to hospital with acute gastroenteritis. In 28 this was transient and settled rapidly, but in the remaining three it indicated a more serious and persistent problem. The most important predisposing factor was viral infection, in particular with rotavirus. The current regimen for the management of sugar intolerance complicating acute gastroenteritis at this hospital is outlined.

A prospective study of delayed recovery after acute gastroenteritis in childhood was undertaken in the gastroenteritis unit at this hospital in 1973.¹ Seventy four children out of a total of 348 (21.2%) admitted with acute gastroenteritis were found to have delayed recovery. One of the three categories of delayed recovery described was disaccharide intolerance, implying watery diarrhoea with excess stool reducing sugars. Disaccharide intolerance was diagnosed in 38 children (10.9%) and it was found that a number of factors predisposed to this complication. These were age less than 2 months, male sex, Asian origin, weight below the 3rd centile, and bottle feeding.

Since that time there have been important advances in our knowledge of the aetiology of gastroenteritis, and also changes in infant feeding practice. It is now possible to identify a variety of stool viruses by electron microscopy, and bottle fed infants have been changed from high solute cows' milk feeds to low solute milks. This change has already had a notable effect on the clinical manifestations of acute gastroenteritis, for example a virtual disappearance of severe hypernatraemia.² We have undertaken a further, prospective study of sugar intolerance complicating acute gastroenteritis, have related this to aetiology in a manner not possible in the earlier study, and have reviewed those factors predisposing to this condition.

Patients and methods

Two hundred consecutive children admitted to this hospital with acute gastroenteritis were studied prospectively using a computer programme. Details

of age, sex, ethnic origin, nutrition, mode of feeding, and management were collected, as well as stool pathogens. Most children were managed with an oral glucose electrolyte preparation for 24 hours, and then their appropriate milk and solid food (if applicable) were reintroduced over a period of four days. Those who were 5% or more dehydrated were treated with intravenous fluids, then oral glucose electrolyte mixture followed by reintroduction of normal feeding. If diarrhoea recurred or persisted on this oral regimen and the stools were watery, the watery portion of the stool was tested with Clinitest tablets.³ If 0.5% or more reducing substances was found, the clinical diagnosis of sugar intolerance was made. The diagnosis was disaccharide (lactose) intolerance if this occurred while the child was having a diet containing lactose, or monosaccharide intolerance if the child was still having a glucose electrolyte mixture. In the former case, when there was a definite exacerbation of diarrhoea, the infant returned to glucose electrolyte mixture for another 24 hours before a further attempt was made to reintroduce normal feeds. If diarrhoea with reducing substances recurred a second time, the infant was returned yet again to the glucose electrolyte mixture. If a relapse of diarrhoea occurred on a third attempt at reintroducing a cows' milk formula, a small intestinal biopsy was performed. Where an enteropathy was present, a provisional diagnosis of cows' milk sensitive enteropathy was made and Pregestimil with a cows' milk free diet was begun. If the mucosa was normal, the infant was again returned to its normal diet. In the latter case, if diarrhoea persisted or was exacerbated while taking a glucose electrolyte mixture, then a

diagnosis of monosaccharide intolerance was made and each infant was either given an electrolyte mixture for 24 hours (being closely observed for hypoglycaemia) or if the diarrhoea was more severe and hydration compromised then intravenous fluids were administered for 24 hours. The infant was then returned to an oral glucose electrolyte mixture with progression to normal diet. Some children were already on Pregestimil when they developed acute gastroenteritis, and after a period on glucose electrolyte mixture were again given Pregestimil. If they had watery stools with excess reducing substances, glucose or glucose polymer intolerance was diagnosed, and they were managed as above.

Daily stool cultures for bacterial pathogens were performed in most children, and stool electron microscopy for viruses was performed once, 24 hours after admission when possible. All clinical and laboratory data were compiled on a computer questionnaire and then sent to the University of London Computer Centre for computing and analysis. Statistical significance was assessed using the χ^2 test with one degree of freedom.

Results

Sugar intolerance was diagnosed in 31 of the 200 (15.5%) children observed. Fifteen were lactose intolerant (7.5%) and 16 were glucose intolerant (8%).

Age and sex. One hundred and seventy seven of the 200 children were under 2 years old, and 86 (43%) were aged under 6 months. There was a clear male preponderance, with 120 boys and 80 girls. All except one of the children with sugar intolerance were under 2 years of age, and most were under 18 months. Eleven of the 15 children with disaccharide intolerance were under 6 months of age, whereas only two of the 16 infants with monosaccharide intolerance were under 6 months (Fig. 1). The male preponderance was accentuated in the sugar intolerant group—74.2% were boys compared to 60% in the group as a whole, although this difference is not statistically significant.

Nutrition (Fig. 2). When children were grouped in relation to weight centiles on admission to hospital, the finding of sugar intolerance occurred in proportion to the centile category in the group as a whole.

Ethnic origin (Table 1). Caucasian infants accounted for the largest number of admissions. In the sugar intolerant group there was a relative increase in the representation of children originating from the Indian subcontinent, although this was not statistically significant.

Fig. 1 Relative frequencies of monosaccharide and disaccharide intolerance in relation to age.

Fig. 2 Weight centiles on admission to hospital with acute gastroenteritis.

Table 1 Ethnic origin of 200 sugar tolerant (n=169) and intolerant (n=31) children admitted to hospital with acute gastroenteritis

	Sugar tolerant (%)	Sugar intolerant (%)
Caucasian	96 (56.8)	15 (48.4)
African	10 (5.9)	1 (3.2)
West Indian	13 (7.7)	2 (6.5)
Indian subcontinent	36 (21.3)	9 (29)
Oriental	2 (1.2)	0
Mixed	10 (5.9)	3 (9.7)
Other	2 (1.2)	1 (3.2)

% Values refer to the total in each group.

χ^2 analysis shows no significant difference for any ethnic group.

Breastfeeding. Of the 200 infants admitted with gastroenteritis, 33% had been breastfed for at least four weeks: 27% of the sugar intolerant children had been breastfed for such a period.

Aetiological studies

Stool viruses (Table 2)

In the group as a whole, rotavirus was identified in 45 of the 166 (27.1%) infants whose stools had been examined by electron microscopy. It was seen in 51.7% of infants with sugar intolerance but in only 21% without this complication. This difference is highly significant ($P=0.001$). No other virus predisposed to sugar intolerance, but the numbers are small. Even grouping all the other viruses as one, there is no significant difference between the sugar tolerant and intolerant groups. Fifteen of the 45 children with rotavirus (33%) developed sugar intolerance—nine of these were monosaccharide intolerant and six disaccharide intolerant.

Bacterial pathogens in stool (Table 3)

Bacterial pathogens were found in the same proportion in the sugar intolerant children as in the group as a whole.

Stool viruses and bacteria

Nine of the 200 children had coexistent viral and bacterial pathogens. These were rotavirus in six, calici in two, and astrovirus in one. The bacteria were enteropathogenic *Escherichia coli* (conventional serotypes) in seven, campylobacter in two and salmonella in one (one child had *E coli* and campylobacter together). Two of the sugar intolerant children had a virus and bacterium together; both had rotavirus, one with an *E coli* and the other with a salmonella. One child had rotavirus associ-

Table 3 Stool bacterial culture in 200 sugar tolerant ($n=169$) and intolerant ($n=31$) children admitted to hospital with acute gastroenteritis

	Sugar tolerant (%)	Sugar intolerant (%)
Enteropathogenic		
<i>Escherichia coli</i>	16 (9.9)	3 (9.1)
Salmonella	14 (8.6)	2 (6.1)
Shigella	2 (1.2)	0
Campylobacter	9* (5.6)	2† (6.1)
Other	1‡ (0.6)	0
No growth	120 (74.1)	26 (78.7)
Not done	9	0
Overall positive	40 (25)	5 (16.1)

*Both times associated with *E coli*.

†Both with other pathogens—*E coli* in one, salmonella in the other.

‡*Pseudomonas aeruginosa*.

% values refer to the total in each group who had stool bacterial culture performed.

Using χ^2 test there was no significant difference for any pathogen.

ated with candida in the stool. More than one virus was found in three children, none of whom had sugar intolerance. In two, astrovirus and rotavirus were seen together and in the other small round virus (SRV) was seen with adenovirus. Of the children who had both stool culture and electron microscopy performed in the total group, 99 of 166 (59.6%) had a pathogen identified, compared with 21 of 29 (72.4%) in children who were sugar intolerant. One child with disaccharide intolerance had *Giardia lamblia* but no other infective agent in the stool; he was the only child with this infection in the group as a whole.

Management. Twenty two of the sugar intolerant children were given oral treatment as outlined above. Nine children with glucose intolerance required intravenous infusion because of recurrence of severe diarrhoea and one of these required intravenous alimentation. In nine children, normal diet was reintroduced only once, and in 16 twice, before they became tolerant of sugars. Of the six children requiring a third reintroduction, three tolerated it. In the remaining three who did not, a small intestinal biopsy was performed, the indication being diarrhoea and sugar intolerance persisting for more than two weeks. In all cases there was a small intestinal enteropathy of varying severity. Two responded to Pregestimil and a cows' milk free diet and have subsequently returned to a normal diet. The third was intravenously fed for two weeks, after which a normal diet was reintroduced successfully, the small intestinal mucosa having shown only minor abnormalities.

In those infants with an enteropathy, it is our policy to continue a diet free of cows' milk until the

Table 2 Viruses identified in stool by electron microscopy in 200 sugar tolerant ($n=164$) and intolerant ($n=31$) children admitted to hospital with acute gastroenteritis

	Sugar tolerant (%)	Sugar intolerant (%)	χ^2 test
Rotavirus	30 (21)	15 (51.7)	$P=0.001$
Adenovirus	17 (12.2)	1 (3.4)	ns
Astrovirus	2 (1.4)	1 (3.4)	ns
Calici	5 (3.6)	0	ns
Small round virus	4 (2.9)	0	ns
Negative	82 (58.6)	12 (41.4)	
Not done	32	2	
Overall positive	55* (40.1)	17 (58.6)	

*3 had more than one virus.

ns=Not significant.

% values refer to the total in each group who had electron microscopy performed.

Fig. 3 Time of developing sugar intolerance after reintroducing milk (disaccharide intolerance). (Comparison between present study and that of Gribbin *et al.*)¹

Histogram relating to Gribbin's study reproduced by permission of Acta Paediatrica Belgica.

age of 9 months to 1 year. The child is then admitted to hospital for challenge, firstly with lactose and then with increasing amounts of cows' milk. Hospital admission is deemed necessary not only to permit more accurate observation but also because of the possibility, albeit rare, of an anaphylactic reaction.⁴ The small minority who fail this cows' milk challenge resume a cows' milk free diet, and the diagnosis may have to be reconsidered.

Time interval before development of disaccharide intolerance. Disaccharide intolerance occurred within five days of reintroducing cows' milk in the 15 infants. In general, this was much earlier than in Gribbin's study¹ to which we have previously referred (Fig. 3).

Discussion

This study again shows that in infants with acute gastroenteritis severe enough to merit hospital admission, transient sugar intolerance is a common complication, affecting 28 of 200 (14%) children in this study. Among the factors that seemed to predispose to sugar intolerance, the foremost is viral infection, and the rotavirus in particular was implicated. Rotavirus was detected by electron microscopy in the stools of 51.7% of the sugar intolerant children. Shepherd first reported transient sugar intolerance as a complication of rotavirus infection in 2 of 30 children,⁵ but Manuel *et al.*⁶ suggested that the problem was rather more common—rotavirus was identified in six of nine children with

transient monosaccharide intolerance in his study. Active glucose absorption from the small intestinal lumen is coupled with that of sodium⁷ and depends on the sodium pump, that is the enzyme $\text{Na}^+ - \text{K}^+ - \text{ATPase}$. Deficient intracellular activity of this enzyme has been shown in the ileum of piglets infected with coronavirus.⁸ The same mechanism, with impairment of active sodium transport is thought to explain the transient glucose malabsorption in infants with rotavirus infection. No other infective agent showed a statistically significant relation with sugar intolerance.

Gribbin¹ showed that over 75% of the children with sugar intolerance in her study were aged under 2 months. Although we found sugar intolerance more frequently in the younger child, this was in proportion to the increased incidence of gastroenteritis in the early months of life. There was, however, a noticeable split in the relative frequencies of mono- and disaccharide intolerance with age—11 of 15 children with disaccharide intolerance were less than 6 months old, whereas 14 of 16 with monosaccharide intolerance were over 6 months of age. There was no clear explanation for this difference. Of our three infants who underwent small intestinal biopsy, the one with disaccharide intolerance had low disaccharidase activities but an almost normal histological appearance, whereas the two with monosaccharide intolerance had normal disaccharidase values, but in one case more obvious histological abnormalities. This is in accord with the observation that mucosal damage, as assessed by light microscopy, does not correlate accurately with disaccharidase values.⁹

Even allowing for gastroenteritis being more common in boys (boy:girl ratio in the total group was 3:2), sugar intolerance seems to be more prevalent in boys with a ratio of 23:8. Manuel noted a similar preponderance of boys in a study of monosaccharide intolerance complicating acute gastroenteritis.⁶

Although a greater proportion of sugar intolerant children were of Asian origin and had a weight less than the 3rd centile, the numbers were too small for these factors to be considered significant. One third of the group as a whole had been breast fed for more than four weeks compared with 27% of the sugar intolerant children. It is well recognised that breast-feeding increases resistance to gastroenteritis in the infant, but our study suggests that it gives no significant protection against sugar intolerance.

As mentioned above, all but one of our 15 children with disaccharide intolerance developed sugar malabsorption within four days of the reintroduction of lactose. This contrasts with Gribbin's study,¹ where intolerance developed up to 34 days

after reintroducing milk. There has been a considerable change in infant feeding practices since Gribbin's study in 1973, at which time the infants were reintroduced to high solute feeds such as ½ cream Cow and Gate formula. There is evidence that these milks are more sensitising than the present low solute equivalents. In the guinea pig fed on cows' milk, anaphylactic sensitivity develops rapidly, whereas low solute preparations are rarely associated with this.¹⁰ The sugar intolerance Gribbin observed may have been related to cows' milk protein intolerance in many cases,¹¹ which is a different entity to the early onset transient sugar intolerance described in this study.

Transient sugar intolerance complicating acute gastroenteritis should be recognised as a separate condition to the postenteritis syndrome with persistent lactose or cows' milk protein intolerance, or both, which may give rise to chronic diarrhoea and failure to thrive. The child with acute gastroenteritis who has an exacerbation of diarrhoea associated with sugar in the stools while being reintroduced to milk should be offered at least a second, and even a third, attempt at reintroduction; the alternative is a 24 hour period of intravenous fluids with nil by mouth followed by a formal reintroduction. In most the problem will resolve if this regimen is adopted. This approach is preferable to the prescription of a lactose free diet in these circumstances. Our regimen must be approached with some circumspection, however, in a previously malnourished child. In only 10% of those with sugar intolerance (3 of 31 in our study) was this a manifestation of a more serious and persistent problem requiring a change to a milk free of lactose and cows' milk protein.

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