Disordered small intestinal motility: a rational basis for toddlers' diarrhoea

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SUMMARY Toddler diarrhoea is the commonest cause of chronic diarrhoea without failure to thrive in childhood, but its pathogenesis remains obscure. We have studied upper small intestinal motility in three groups of children (control group 1 – children with no intestinal pathology undergoing duodenal intubation, $n=6$; control group 2 – children with gastrointestinal pathology other than toddler diarrhoea, $n=11$; control group 3 – children with toddler diarrhoea, $n=8$). We studied fasting motor patterns and the response of the migrating motor complex to intravenous cholecystokinin and an intraduodenal bolus of 5% dextrose. The characteristics of the migrating motor complex in the three groups did not differ but their response to dextrose did. Intraduodenal dextrose disrupted the migrating motor complex in four out of four children in group 1; seven out of nine children in group 2; and nil of eight children with toddler diarrhoea in group 3. We suggest that this failure of intestinal motor response may play a major role in the pathogenesis of the diarrhoea in this condition.

The syndrome described as toddler diarrhoea,¹ chronic non-specific diarrhoea,² or the irritable colon syndrome of childhood³ is the most common cause of chronic diarrhoea without failure to thrive in childhood, yet the pathophysiological mechanisms operating in this condition are largely unknown. Previously this syndrome was considered with other disorders to be part of the idiopathic coeliac syndrome⁴ and it was suggested that food intolerance caused the diarrhoea. The empirical finding, that removal of sugary fruits from,^{1,3} or increasing the fat content of the diet⁵ improved the diarrhoea, appeared to reinforce this view. The presence of undigested food remnants and excess starch granules, however, in the stools of patients with this syndrome³ suggests that small intestinal transit time is decreased^{3,6} and that small intestinal motility may be disordered. The recent recognition of clear cut motility patterns in the small intestine^{7,8} prompted us to examine small intestinal motility in children with toddler diarrhoea.

Methods

METHODS

Three groups of subjects were studied:

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* Since the publication of this paper Professor Harries has sadly died.

Control group 1 (C1)

Three children suspected of having small intestinal pathology undergoing intubation, and three children undergoing pancreatic function tests, who were subsequently found to be normal, aged between 8 months and 11 years (five boys and one girl).

Control group 2 (C2)

Children with proven gastrointestinal disease other than toddler diarrhoea: two with ulcerative colitis, three with 'lethal protracted diarrhoea of infancy',⁹ one with mental retardation and diarrhoea, one with a VIP secreting ganglioneuroma, one with cow's milk protein intolerance, one with multiple food intolerances, one with idiopathic pancreatic insufficiency, and one with Schwachman's syndrome, aged between 4 months and 9 years (seven boys and four girls).

Patients with toddler diarrhoea (TD)

Eight patients, aged between 3.7 and 11.5 years (six boys and two girls).

After an overnight fast the patients were sedated with chlorpromazine (2 mg/kg intramuscularly). A triple lumen catheter was positioned under fluoroscopic control so that the distal port lay in the proximal jejunum, and the proximal two ports in the duodenum. The port holes were 10 cm apart. The tube was perfused with 0.9% saline at a rate of 0.2 ml/min by a pneumohydraulic constant pressure

perfusion pump (Arndorfer Medical Specialties, Wisconsin, USA). The intraluminal pressures were measured by three transducers (Series 3, Luerlock, Gaeltec, UK), the output of which was displayed on an oscillographic chart recorder (Washington MDU-4).

Baseline recordings were made to establish the character of the fasting activity in each individual. Migrating motor complexes (MMCs) were seen as bands of high amplitude rhythmic (11–13 cpm) pressure waves which propagated from the duodenum into the jejunum. (It is possible that the sedation used might affect the MMCs. In a preliminary study, however, the fasting activity has been recorded in eight children six hours and 24–30 hours after sedation. We have been unable to recognise any consistent difference in the variables of the MMCs in each patient at these two times.) When two, or more usually three MMCs had been observed, the ability of the intravenous cholecystokinin or intraduodenal dextrose to disrupt the activity front was tested. When the latest activity front had started in the duodenum and had propagated into the jejunum (as visualised by the record from the distal port) either cholecystokinin (Pancreozymin, Boots UK Ltd) was given as a bolus dose intravenously (0.2 U/kg body weight) or 20 ml of 5% dextrose was introduced into the duodenum as two 10 ml boluses through the proximal port. Disruption of the MMC after such stimuli was said to have occurred if the MMC was foreshortened, and ceased within two minutes of these procedures. For the purposes of comparison all values were

taken from the transducer at the distal port – that is, in the proximal jejunum, as this was the most constant reference point. The recordings were read blind by inspection both by the person performing the test and an independent observer.

Although disruption of the MMC by dextrose seemed obvious to the two observers who were reading the traces, a mathematical quantification of disruption was also devised. Figure 1 shows two MMCs recorded from a single patient. The duration of the last complex, MMC3, is shown as Td and that of the first complex MMC1, as Tn. Clearly Td is much less than Tn and this complex was thought on inspection to have been disrupted by the instillation of dextrose into the duodenum at the time shown (ID Dextrose). Td can be divided into Ta and Tb – that is, the time interval before and after the disrupting stimulus. Clearly the duration of the complex after the stimulus, Tb, should be shorter in those patients in whom the complex has been disrupted, than in those in whom disruption does not occur. It is possible to derive a disruption index having calculated the expected duration of the complex after the stimulus from the value Tn – Ta.

The disruption index =

$$\frac{\text{Observed duration of complex after stimulus}}{\text{Expected duration of complex after stimulus}} = \frac{T_b}{T_n - T_a}$$

The disruption index should be much smaller in those patients in whom disruption has occurred.

This study was approved by the Standing Com-

Fig. 1 Two MMCs recorded from jejunum of single patient one of which has been disrupted by intraduodenal dextrose. For explanation see text.

Table 1 Migrating motor complexes in children and adults

	C1 (n=6)	C2 (n=10)	TD (n=8)	Adults (n=18)
Duration (min)				
Mean $\pm$ SEM	5.5 $\pm$ 0.6	7.1 $\pm$ 1.0	7.2 $\pm$ 2.0	5.90 $\pm$ 0.37
Median	5.9	7.3	5.1	
Interval between MMC (min)				
Mean $\pm$ SEM	99.5 $\pm$ 19.4	68.8 $\pm$ 12.7	68.3 $\pm$ 8.9	112.5 $\pm$ 11.41
Median	93.5	55	68.8	
Propagation velocity (cm/min)				
Mean $\pm$ SEM	29.5 $\pm$ 22.9	8.1 $\pm$ 2.6	17.0 $\pm$ 2.4	11.30 $\pm$ 0.14
Median	33	7	16.6	

There was no statistical significance between the three groups of children.

The adult data are taken from a similar study in a group of unsedated adult patients.⁸

mittee on Ethical Practice of the Hospital for Sick Children, Great Ormond Street, and informed consent was obtained in writing, before starting the procedure, from the patients' parents.

Results

The duration of the MMC, the interval between the MMCs, and the propagation velocity of the MMCs in the three groups are shown in Table 1, together with adult values obtained at the same site by a similar technique.⁹ There is no difference between the three groups (Mann and Whitney U test).

The effect of cholecystokinin in 'physiological' doses is clearly shown in Fig. 2, with abrupt termination of the MMC at all three sites within one minute of the injection. Cholecystokinin disrupted the MMC in four out of four control children. Figure 3 shows the disruption of an MMC in the jejunum by the introduction of dextrose into the duodenum in one 10 cc bolus at a site 15–20 cm proximal to the jejunal port. The distal complex was foreshortened and terminated within two minutes of the instillation of dextrose. Children with toddler diarrhoea differed from the other two groups in their response to the dextrose which failed to disrupt the MMC as shown in Fig. 4.

The mean duration for Ta and Tb are shown in

Fig. 2a Pressure record from normal patient undergoing pancreatic function test. MMC can be seen. All records have the same format. DP=pressure in the proximal duodenum, DD=pressure in the distal duodenum, J=pressure in the proximal jejunum, T=time base; each deflection represents one minute.

Fig. 2b CCK (0.2 U/kg) given intravenously (ivC) caused abrupt termination of MMC in same patient.

Fig. 3a MMC in normal control child.

Fig. 3b Five per cent dextrose instilled into duodenum of same child foreshortened complex in jejunum.

Table 2. There is no difference in the value of T_a for the three groups ($p > 0.5$) indicating standardisation of the timing of the stimulus. There is, however, a significant increase ($p < 0.001$) in the values of T_b between the children with toddler diarrhoea and the two control groups.

The values for the disruption index in each patient

is shown in Fig. 5. In two patients in the control groups and two in the TD group it was possible to test for disruption on two separate occasions. The response was reproducible for each patient. All the values are shown in this Figure. The disruption index clearly separates those patients in whom the MMC appears to be disrupted by the stimulus

Fig. 4a MMC in child with toddler diarrhoea.

Fig. 4b Five per cent dextrose instilled into duodenum of same child failed to disrupt MMC.

applied from those in whom the disruption did not occur. Intraduodenal dextrose caused disruption in four out of four children in group 1, seven out of nine children in group 2, and nil out of eight children with toddler diarrhoea.

Discussion

In recent years two clear cut patterns of small intestinal motility have been described. There is a fasting pattern characterised by recurring migrating motor complexes^{7,8} which is disrupted within two minutes of eating and replaced by random

Table 2 (A) Comparison of values of Ta/Tb in MMCs disrupted by cholecystokinin and dextrose compared with those that were not disrupted by dextrose

		<i>Disrupted MMC</i> <i>(n=16)</i>	<i>Unaffected MMC</i> <i>(n=12)</i>
Ta	$\bar{x}$	1.74	1.83
	SD	1.21	1.46
		NS*	
Tb	$\bar{x}$	1.55	6.09
	SD	0.82	3.30
		p<0.001*	

(B) Comparison of values of Ta/Tb in MMCs disrupted by dextrose compared with those that were not disrupted by dextrose

		<i>Disrupted MMC</i> <i>(n=12)</i>	<i>Unaffected MMC</i> <i>(n=12)</i>
Ta	$\bar{x}$	1.65	1.68
	SD	1.11	1.54
		NS*	
Tb	$\bar{x}$	1.48	6.09
	SD	0.68	3.30
		p<0.001*	

* Student's unpaired *t* test.

Fig. 5 Index of disruption of MMCs in children with toddler diarrhoea and controls. Patients have been grouped according to response to stimulus applied as recorded independently by two observers. Patients from C1 are represented by symbol Δ , from C2 by the symbol $\square$, and those with toddler diarrhoea by $\bullet$.

segmenting activity, the postprandial pattern. The disruption of MMCs by various food and nutrients is well described, with fat being more efficient than other nutrients at initiating postprandial activity.¹⁰⁻¹¹ Although there is movement of luminal contents through the gut during the postprandial phase, this is considerably slower than that seen at times in the fasting period as measured by flow rates¹²⁻¹⁴ and small bowel transit time.¹⁵⁻¹⁷ Migrating motor complexes have been shown to produce maximal flow rates through the gut in animal studies.¹⁸⁻²⁰ It has been suggested that the major function of MMCs is the removal of intestinal contents following the absorption of nutrients, from the small intestine.²¹

Cholecystokinin,²²⁻²³ gastrin,²⁴⁻²⁵ and insulin²⁶⁻²⁷ have all been implicated in the change from the fasting to the postprandial pattern of motility. Of these candidate hormones only cholecystokinin appears, at least in the experimental animal,²² to be associated with disruption of the MMCs in 'physiological' doses although a later report suggests that this effect may be confined to the proximal small intestine.²⁸ Our studies show for the first time that cholecystokinin, in very small doses, has this effect in man. In addition, the direct visualisation of the effect of intraduodenal dextrose on the MMC has shown major differences between children with toddler diarrhoea and controls. The children with toddler diarrhoea fail to disrupt their MMCs in the normal way in response to dextrose. We suggest that the failure to disrupt MMCs accounts for the presence of excess starch and recognisable food remnants in the stools. The reported effects of dietary manipulation – for example, increasing the fat content of a diet – may be explained by the differing abilities of various nutrients to disrupt MMCs and induce postprandial activity. Although in this study we have not examined the disruption of the MMCs by food we speculate that the failure of disruption of the MMC by dextrose may indicate a general failure of normal disruption of the MMCs by food. This would result in a marked increase in the rate of transit of small intestinal contents which might lead to the delivery of partially digested food and excessive quantities of other substances, such as bile salts, to the colon where bacterial degradation may then yield secretagogues, such as hydroxy fatty acids and unconjugated bile salts.

Both hydroxy fatty acids and dihydroxy bile salts have been shown to induce secretion of water and electrolytes in the colon²⁹⁻³⁰ and thus may significantly effect conservation of water and electrolytes by the colon. The diarrhoea may result, therefore, from a disordered colonic function. A recent study of stool composition in children with toddler

diarrhoea shows an increase in sodium, extractable water, and bile salt content.³¹ This study would, therefore, support our hypothesis. A similar decrease in the small bowel transit time postprandially may account for the mechanism of postvagotomy diarrhoea following the observation that the period of postprandial activity is much shorter in the postvagotomy patients with diarrhoea than those without.³²

The reasons for the failure of dextrose to disrupt the MMCs in these patients are unclear. One possible cause could be a failure of a receptor in the duodenum to respond to the dextrose and trigger the normal neurohumeral effector mechanism for disrupting the motor complex in response to food. Abnormalities of small intestinal motility in functional bowel disease have been observed before,³³⁻³⁴ but their significance has not always been clear. The defect in motility reported here, however, could play a major role in the pathogenesis of this condition.

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