Improvement of abnormal lactulose/rhamnose permeability in active Crohn's disease of the small bowel by an elemental diet

I R SANDERSON, P BOULTON, I MENZIES, AND J A WALKER-SMITH

From the Department of Child Health, St Bartholomew's Hospital, and the Institute of Child Health, and the Department of Chemical Pathology, St Thomas' Hospital, London

SUMMARY Intestinal permeability to sugar has been used as an objective measure of small bowel integrity to assess the efficacy of an elemental diet as the sole treatment of Crohn's disease of the small bowel. Fourteen children aged 11–17 years with active small bowel Crohn's disease were given an elemental diet for six weeks. Investigations with iso-osmolar oral test solutions before and after this treatment showed that all 14 children had abnormally raised lactulose/L-rhamnose permeability ratios, which fell significantly after the elemental diet. This change coincided with marked clinical improvement, as assessed by a disease activity index score.

An elemental diet is as effective as high dose steroids in inducing a remission in small bowel Crohn's disease both in adults¹ and in children,² as judged by clinical assessment, a disease activity index score, ESR, CRP, and serum albumin. Elemental diets also reduce the amount of protein loss from inflamed bowel.³ The efficacy of an elemental diet, however, has never been evaluated using an objective index of small bowel integrity. Intestinal permeability can be assessed non-invasively with sugar markers and is abnormal in diseases which affect the morphology of the small intestine such as coeliac disease,⁴ gastroenteritis⁵ and cow's milk hypersensitivity.⁵ Sugar permeability has also been shown to be abnormal in active Crohn's disease.⁶

The aim of this study was to determine what effect, if any, the administration of an elemental diet has upon intestinal sugar permeability tests in children with active Crohn's disease of the small bowel.

Methods

PATIENTS

Children who were in need of therapy for active Crohn's disease of the small bowel were chosen from

the Paediatric Inflammatory Bowel Disease Clinic at St Bartholomew's Hospital, London. The diagnosis was based upon their clinical features, barium follow through, and ileal histology from biopsies taken at colonoscopy.⁷ A Lloyd-Still disease activity index score⁸ was obtained before treatment began (Table 1) and assessed again after six weeks. The percentage score (a normal child scoring 100 points) is made up as follows: symptoms – 10; radiology – 15; examination – 30; haemoglobin white cell count, albumin, ESR – 25; height and weight – 20. Making a total of 100 points. Radiology was not repeated after six weeks and so was not included in assessing any change over the six week period. Seven of the children with active disease were on steroids at the time of their attendance at the clinic. The dosage was reduced when put on the elemental diet (Table 1). Six children (Table 2) referred as suspected chronic inflammatory bowel disease were also studied. After investigation including colonoscopy, they proved to have no recognisable disease in small intestine and acted as controls.

ELEMENTAL DIET

The children with active Crohn's disease of the small bowel were given an elemental diet, Flexical[®] (Bristol-Myers) through a nasogastric tube;² the daily amount was determined using the recommended

Address for correspondence: Dr I R Sanderson, Queen Elizabeth Hospital for Children, Hackney Road, London E2 8PS.

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Table 1 Sex, age, Lloyd-Still disease activity score and Prednisolone therapy before and after treatment with an elemental diet

Name	Sex	Age	Score	Prednisone mean daily dose/mg	
				(Before)	(6 weeks)
PD	M	11.2	67	0	0
AN	F	11.4	48	0	0
MD	F	11.9	58	10	1.25
MC	M	12.6	67	7.5	0
CC	F	12.7	38	0	0
AM	M	12.8	75	10	3.75
MD	M	12.8	62	0	0
KC	M	13.3	68	0	0
MV	M	13.8	51	25	10
LP	M	14.5	56	0	0
JH	F	15.2	66	30	10
GH	M	15.9	75	20	3.25
PH	M	16.0	63	0	0
DB	F	17.2	57	13.75	0

daily allowance based on the age of the child.⁹ They were otherwise given nil by mouth for six weeks and then foods were introduced sequentially in a controlled manner.²

SUGAR PERMEABILITY STUDIES

After an overnight fast of six hours a 80 ml solution containing 5.25 g of lactulose and 0.75 g of rhamnose (260 mmol/kg) was given to the child. All the urine passed in the subsequent five hours was collected, the volume recorded and an aliquot preserved with merthiolate (100 mg/100 ml minimum) for analysis.

Urine sugars were estimated by quantitative thin layer chromatography.¹⁰ After development of duplicate chromatograms using appropriate solvent systems, and a four aminobenzoic/phosphoric acid colour reaction, peak heights of the separated sugar zones were measured by scanning densitometry and corrected to a constant internal standard value. Sugar concentrations were then read by interpolation from standard curves plotted from the same chromatogram. Details of the technique and modifications used are given elsewhere.^{10,11} The method is accurate and sensitive, and precision between 2 and 8%

Table 2 Sex, age and reason for referral of children who acted as controls

Name	Sex	Age	Diagnosis
TE	F	8.9	Juvenile rectal polyp
PM	M	11.1	Recurrent abdominal pain of childhood
SGS	M	13.2	Recurrent abdominal pain of childhood
KH	F	14.7	Recurrent abdominal pain of childhood
HS	F	15.6	Ulcerative colitis
HS	F	15.6	Ulcerative colitis
SH	M	17.9	Crohn's colitis

(coefficient of variation) without replication over the concentration range encountered.¹¹ Intestinal lactulose/rhamnose permeation was expressed as a ratio of the ingested dose for each sugar excreted in the five hour urine collection.

STATISTICAL ANALYSIS

Results were analysed using the paired Student's *t* test.

Results

The six control children in whom chronic inflammatory bowel disease had been excluded had lactulose/rhamnose permeability ratios within the normal range (Figure) as delineated in healthy children by Beach *et al*¹² (0.04 ± 0.01 , mean $\pm$ standard deviation, ratio of percentage of oral dose excreted in five hour urine).

All 14 children with Crohn's disease of the small bowel showed an abnormally raised sugar permeability ratio (0.256 ± 0.037) before treatment. After

Figure Lactulose rhamnose ratios in 14 children with active Crohn's disease of the small bowel before and after a six week period of feeding with an elemental diet.

treatment with an elemental diet there was a significant fall ($p<0.001$) in the sugar permeability ratio in all children to 0.093 ± 0.012 (Figure) despite receiving no other added therapy. Seven of the patients had lactulose/rhamnose permeability ratios within the normal range after six weeks dietary therapy.

The improvement in the intestinal permeability corresponded with other indices of disease activity such as the ESR, body weight and Lloyd-Still disease activity index (Table 3).

Discussion

Although the pathways of intestinal sugar permeation and mechanisms of altered permeability have not yet been fully characterised,¹³ the ratio of unmediated disaccharide/monosaccharide permeation is known to be raised in conditions associated with small intestinal mucosal damage such as coeliac disease,^{4,14} tropical sprue,¹⁵ and rotavirus enteritis.¹¹ A correlation between morphological changes in the small intestinal mucosa and the lactulose/rhamnose permeability ratio has also been shown,⁵ and differential sugar permeation is now widely used as an objective index of small intestinal integrity.¹³

Abnormal intestinal permeability to sugar markers was first demonstrated in Crohn's disease by Pearson *et al*⁶ who noted a relative increase in the permeation of lactulose compared with that of mannitol. A comparable abnormality has been demonstrated during the present study, all untreated patients having lactulose/rhamnose permeability ratios above the normal range. It is of interest that those children with chronic inflammatory bowel disease confined to the large intestine had permeability ratios within the normal range as defined by Beach *et al*,¹²

and they were therefore considered suitable to serve as control subjects (Table 2). This is possibly because the sugar markers become degraded by bacteria on reaching the large intestine, or because the large bowel represents a relatively small mucosal surface area compared with the small bowel.

Other probe-markers of intestinal permeability such as ⁵¹chromium-EDTA¹⁶ and polyethylene glycol 400¹⁷ have also been used to study active Crohn's disease, but the technique has not previously been used to assess the effect of an elemental diet in this condition. All the patients showed an improvement after receiving an elemental diet, and at least half achieved normal lactulose/rhamnose permeability ratios at end of the dietary period. This indicates that the increased intestinal permeability seen in this condition is a secondary rather than a primary phenomenon, and is therefore unlikely to represent a factor predisposing to the development of Crohn's disease as has been previously suggested.¹⁸

In conclusion, this study shows for the first time that an elemental diet has a direct effect on the small intestine of patients with Crohn's disease and does not merely induce a general improvement in their nutritional state.

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Table 3 Changes in indicators of disease activity over the six weeks on an elemental diet

	Changes over the six week period of elemental diet		
	Disease activity score (%)	ESR (mm/h)	Weight (kg)
PD	+18	-30	+3.2
AN	+32	-43	+5.4
MD	+27	-13	+4.5
MC	+13	-1	+2.0
CC	+20	-12	+2.5
AM	+5	-3	+7.8
MD	+18	-16	+6.4
KC	+17	-22	+0.9
MV	+21	-12	-1.1
LP	+29	-21	+4.0
JH	+10	0	+1.5
GH	+10	+4	+5.6
PH	+22	-17	+1.1
DB	+23	-3	+3.3

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