

Improvement in intestinal permeability with elemental diet treatment in Crohn's disease

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Intestinal permeability was assessed in patients with small bowel Crohn's disease by measuring lactulose/mannitol ratio before and after treatment with elemental diet. Ten patients had abnormal intestinal permeability with a significantly higher mean 6 hours urinary lactulose recovery and mean lactulose: mannitol ratio compared with controls. Treatment with elemental diet lead to symptomatic improvement in all patients and an improvement in permeability with a significant reduction in the mean 6 hours urinary recovery of lactulose (from 0.73+0.33 to 0.45±0.25; paired t-test p<0.01) and in the lactulose: mannitol ratio (from 0.053±0.023 to 0.028±0.017; paired t-test: p<.05). This study shows that the symptomatic improvement in patients with Crohn's disease brought about by treatment with an elemental diet is associated with objective evidence of mucosal healing assessed by measurement of the barrier function of the small bowel mucosa.
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Key Words: Intestinal permeability, Crohn's disease, Elemental diet

The normal small intestinal mucosa acts as a protective barrier excluding most molecules except water, electrolytes and the products of digestion (1-3). However when its structure and/or function is disrupted, as in active Crohn's disease, its permeability to normally excluded molecules increases (4,5). Measurement of the permeation of such molecules will reflect the extent and severity of mucosal disruption (3). Serial measurements in patients with active Crohn's disease may allow the response, or healing, of the disrupted mucose during treatment to be assessed (6,7).

Such tests often use two probes, a small sugar such as mannitol (radi <0.4 nm) which is partially absorbed, probably via small transcellular channels of high incidence, and a larger disaccharide such as lactulose (radi>0.5 nm) which is believed to be absorbed via larger intercellular channels of low incidence (2). Villous damage in Coeliac disease increases absorption of the larger probe through the intercellular tight junctions but reduces the absorption of the smaller probe, probabllp as a results of a loss of total cell surface area (8). Any water soluble probes of ap-

propriate size may be used in these tests of intestinal permeability provided that they are not metabolised and that after absorption they are regularly and uniformly excreted by the kidneys (1). Urinary recovery of the test probe will therefore be equivalent to its intestinal absorption (2). The aim of this study was to see, if treatment of active small bowel Crohn's disease with elemental diet (3) leads to an improvement in intestinal damage as reflected by an intestinal permeability test.

MATERIALS AND METHODS

Patients. 10 patients (6 female, 4 male; age range 22-38 years) with symptomatic Crohn's disease confined to the small bowel (terminal ileitis) as shown by indium-111 leucocyte scintigraphy were studied before and after treatment with an elemental diet. During treatment only elemental diet (E028, Scientific Hospital Supplies Ltd, Liverpool UK) was taken, all other food was forbidden and any drug treatment was withdrawn. Treatment with E028 was continued until the patient was asymptomatic (3).

Normal subjects. 15 healthy volunteers (10 male, 5 female; age range 24-48 years) were studied, 6 of them have the test twice a fortnight apart to assess test reproducibility.

Intestinal permeability test. A 50 ml solution containing 5 g lactulose and 1 g mannitol in water (osmolarity 400 mosmo/L) was drunk after a overnight

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Table 1. Intra-subject reproducibility of the 5 g lactulose, 1 g mannitol intestinal permeability test. Urinary 6 hours lactulose: mannitol recovery ratios given for two tests performed 2 weeks apart

Subject	1st Test	2nd Test
1	.01	.01
2	.02	.02
3	.02	.02
4	.06	.03
5	.03	.03
6	.02	.02

fast. After 1 hour the subject was encouraged to drink liberally and after 2 hours allowed to eat. A pretest sample of urine was collected and subsequently a 6 hour urine collection made in a bottle containing 1 ml 20% chlorhexidine and the volume recorded. After thorough mixing two 25 ml aliquots of urine were taken and, together with the pretest sample, frozen until assayed. Urinary lactulose and mannitol were assayed as described by Northop et al in 1989 and Lunn et al in 1989 respectively (9,10). Results were expressed both as percent at 6 hours urinary recovery of each probe and as a lactulose: mannitol recovery ratio.

RESULTS

Intra-subject reproducibility of the test was excellent (Table 1) in all but one subject. The patients had prior

to treatment, abnormal intestinal permeability (Table 2 and 3) with a significantly higher mean 6 hours urinary lactulose recovery and mean lactulose: mannitol ratio. Treatment with elemental diet lead to symptomatic improvement in all patients and an improvement in permeability with a significant reduction in the mean 6 hours urinary recovery of lactulose (from 0.73 ± 0.33 to 0.45 ± 0.25 ; paired t-test: $p < 0.01$) and in the lactulose: mannitol ratio (from 0.053 ± 0.023 to 0.028 ± 0.017 ; paired t-test: $p < 0.05$) (Fig. 1).

DISCUSSION

This study shows that the intestinal permeability test used in a useful and reproducible technique for assessing small bowel mucosal integrity. There were, compared with controls, significant increases in the mean 6 hours urinary lactulose recovery and the mean 6 hours urinary lactulose: mannitol ratio in patients with active Crohn's disease involving the small bowel. There were no consistent changes in these measurements in patients with colonic disease alone. This is presumably because of degradation of the probes by the colonic faecal flora limiting availability for absorption and possibly because of the relatively much smaller area of the colon compared with the small bowel. Colonic disease may have to be extensive and proximal before any abnormality of probe absorption is detected. Mean mannitol recovery was not significantly influenced by Crohn's disease. Mannitol absorption may occur predominantly in the jejunum whilst lac-

Table 2. 6 hours urinary recoveries of lactulose, mannitol and lactulose: mannitol ratio (mean+SD) in controls and patients with ileal Crohn's disease

	n	% lactulose	% mannitol	L:M ratio
Controls	15	0.33 ± 0.21	12.7 ± 7.2	(N.S.)
ileal disease	10	$0.73 \pm 0.33^*$	13.7 ± 2.0	$.05 \pm 0.2^*$

(Comparison with control values: t-test: * $p < 0.001$;
N.S.: $p > 0.05$. Mann Whitney U Test: $^*p < 0.05$; N.S.: $p > 0.05$)

Table 3. 6 hours urinary recovery of lactulose and mannitol and urinary lactulose: mannitol ratios before and after bowel rest in 10 patients with small bowel Crohn's disease

Patients	T	Before Bowel Rest			After Bowel Rest		
		% L	% M	L:M	% L	% M	L:M
1	14	1.06	14.1	.075	.60	15.0	.040
2	24	.76	15.1	.050	.42	57.8	.007
3	8	.26	9.8	.027	.14	24.6	.006
4	17	.34	17.4	.020	.11	5.0	.022
5	10	1.29	14.4	.090	.96	26.9	.036
6	16	.74	13.3	.056	.42	10.8	.039
7	8	.39	13.9	.028	.53	15.2	.035
8	24	.67	12.4	.054	.37	15.2	.024
9	41	.80	12.2	.066	.32	31.6	.010
10	12	.94	14.2	.066	.65	11.2	.058
Mean±S.D.	17±10	.73±33	13.7±2.0	.053±0.023	.45±.25*	21.3±5.2 [†]	.028±.017*

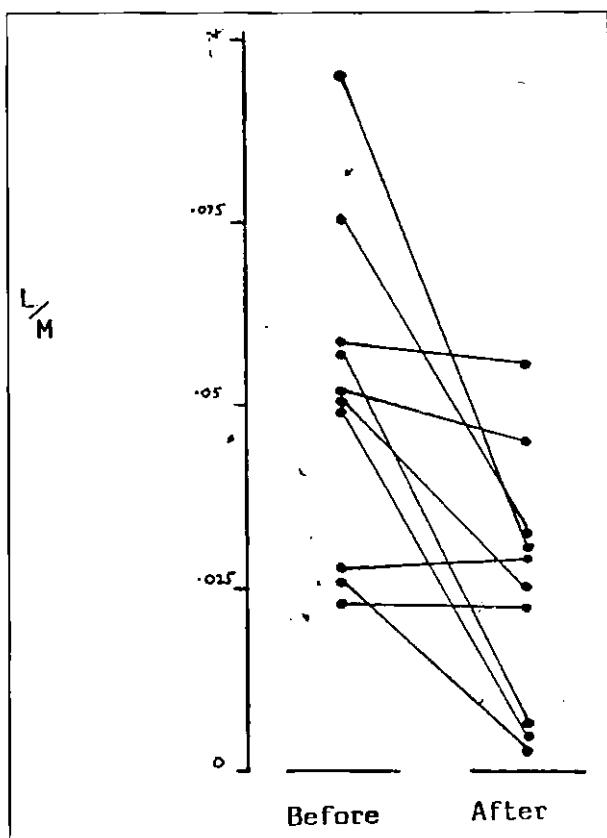


Figure 1. Intestinal permeability (6 h urinary recovery ratio of lactulose: mannitol) before and after bowel rest

tulose is absorbed more uniformly along the small bowel (11,12). Crohn's disease is more likely to affect the distal small bowel (although coexistent mild abnormalities of the proximal small bowel are common) and may predominantly affect lactulose permeation (13). In addition, it is conceivable that in the presence of minor proximal small bowel mucosal damage any increase in mannitol permeability may be counterbalanced by an associated reduction in cell surface area. It is possible therefore that the use of two, rather than a single, probe does not improve discrimination between patients and controls as it does in Coeliac disease (8), a condition predominantly affecting the proximal small bowel and which leads to reduced mannitol permeation because of a gross loss of proximal small bowel surface area (1,12). However, in routine practice the use of two probes which assessing Crohn's disease may be useful allowing some correction for errors in urine collection or intersubject variability in gastrointestinal transit or renal function.

The test was highly reproducible in all, but one of the six controls performing two studies a fortnight apart. The cause of the single discrepancy is unknown. Sequential measurements of intestinal permeability are unlikely to reflect changes in colonic mucosal integrity if changes in the colonic faecal flora

occur between measurement. Similar considerations may apply to the assessment of small bowel mucosal integrity in patients with small bowel colonisation.

The automated enzymatic assays available for this study are an improvement on the previously used methods, being simple, rapid and more precise. However no attempt was made to correct for the small amount of endogenously produced mannitol appearing in the urine (9). The mannitol concentration, when detected, in the pre-test urine sample was much lower than that in the test sample and the relationship between the concentration in the pre-test sample (an early morning urine sample) and that which would occur during the test period when the subject was drinking and eating was unknown.

There was no significant correlation between the 6 hours urinary lactulose: mannitol ratio and the serum orosomucoid concentration in the patients with solely or predominantly small bowel disease. This may not be unexpected as the physical basis of the increased intestinal permeability in Crohn's disease is uncertain. Certainly probes may enter where the mucosa is ulcerated or disrupted. However studies of rat ileal loops (14) in which inflammation has been induced by infection with *N.braziliensis* indicate that the inflammatory response is associated with increased permeability of the intercellular tight-junctions in the crypts. Increased enterocyte turnover as a result of villous enterocyte loss leads to the production of immature enterocytes in the crypts which have less well-developed tight-junctions. In addition, orosomucoid concentrations will reflect transmural, rather than solely mucosal inflammation, and will be equally affected by inflammation along the gastrointestinal tract whereas lactulose and mannitol absorption are predominantly from the small bowel.

It was able to discriminate between healthy volunteers and patients with active small bowel Crohn's disease. The automated enzymatic assays used in this study are an improvement a previously used chromatographic techniques being simple, rapid and more precise. However, alternative simple techniques utilising radiolabeled probes are also available (7) although these involve a small radiation dosage to the subject.

This study shows that the symptomatic improvement in patients with Crohn's disease brought about by treatment with bowel rest and an elemental diet (15) is associated with objective evidence of mucosal healing as assessed by measurement of the barrier function of the small bowel mucosa. This, and a similar study in children (16) and in adults (17), do not indicate how bowel rest and an elemental diet exert their beneficial effect and the elucidation of the mode of action is the object of ongoing studies (18).

Crohn hastalığında elemental diet ile intestinal permeabilitenin düzeldiğinin gösterilmesi

Intestinal perméabilité ince barsak hastalıklarında aktivite ve remisyonlarındaki bilgi verebilen noninvaziv bir test olarak kullanılmaktadır. Elemental diet, ince barsak istirahatı sağlayarak özellikle Crohn hastalığında remisyona yol açan bir tedavi yöntemidir. Tedavi öncesi intestinal perméabilité ölçümü yapılan 10 aktif ince barsak Crohn hastası ve 15 normal sağlıklı kişi incelendi. Hastalara elemental diet tedavisi uygulandı ve ortalama iki hafta içerisinde remisyon ve klinik iyilik sağlandı. Tedavi sonrası yapılan teste 6 saatlik ortalama idrar lactuloz düzeyi 0.73 ± 0.33 'den 0.45 ± 0.25 'e ($p < 0.01$) ve lactuloz/mannitol oranı 0.053 ± 0.023 'den 0.028 ± 0.017 'ye ($p < .05$) düştü. Bu sonuçlar elemental diet uygulamasının ince barsak istirahatını sağlayarak klinik iyilik ve remisyona yol açtığını, ince barsak permeabilitesinin klinik düzelmeye ilgili olarak normale döndüğünü göstermesi açısından önemli bulunumuştur.

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