Intestinal permeability to polyethyleneglycol 600 in Crohn's disease. Peroperative determination in a defined segment of the small intestine

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SUMMARY Ileal permeability to different sized polyethyleneglycols (590–942 dalton PEG) was investigated peroperatively in 11 patients with Crohn's disease and seven with colonic carcinoma. A 15 cm ileal segment was converted into a tied loop, in which the PEG's were deposited. Absorption from the ileal segment was then measured as six-hour urinary recovery of the PEG dose. Polyethyleneglycol absorption in Crohn's disease was greater than in cancer patients and similar throughout the weight range, but in the cancer patients it was inversely proportional to molecular weight. Thus there was significantly greater absorption of the higher weights (≥ 678 dalton) in the Crohn's, than in the cancer patients. The apparently increased permeability of the small intestine in Crohn's disease may be an important factor in its pathogenesis.

Increased intestinal permeability has been suggested as an important pathogenic factor in Crohn's disease.^{1–4} Information on gastrointestinal permeability in Crohn's disease is scanty, however. In some studies different probe molecules were given by mouth, but the observations were conflicting maybe because the part of the gastrointestinal tract in which the probes were absorbed was not defined. To our knowledge, absorption from a defined intestinal segment has not previously been investigated in Crohn's disease.

We therefore measured the permeability of ileal segments during surgery for Crohn's disease or for colonic carcinoma. The test substance was a mixture of different sized polyethyleneglycols.

Methods

PATIENTS

Seven men and four women with Crohn's disease were investigated. Their age range was 18–49 (mean 32) years. The diagnosis was based on classic radiographic findings and Morson's histological criteria. Ileal inflammation was macroscopically and micro-

scopically manifest in all cases, with no major differences between the different patients. Primary ileocaecal resection was planned for nine patients. The other two had already undergone such surgery (including 50–60 cm distal ileum), but recurrent preanastomotic disease necessitated revision. The colon carcinoma group comprised three men and four women, aged 30–82 (mean 67) years. All were to undergo right sided hemicolectomy, and all had normal ileum. All had normal serum kreatinin values and no signs of renal disease. The study was approved by the hospital's Ethical Committee.

INTRAOPERATIVE PROCEDURE

The abdomen was opened and explored. A 15 cm segment of the most distal part of the ileum (measured at the mesenteric margin) was isolated between double ligatures, for conversion into a tied loop. Before the oral ligatures were tied, a fine catheter (Charrière 8) was inserted into the segment through an incision proximal to the loop. Polyethyleneglycol with average weight 600 (PEG 600; HO-(CH₂-CH₂O)_nH, n=13–21), supplied as Macrogolum by Apoteksbolaget, Sweden, was used as the marker of intestinal permeability. Through the catheter, 4 g PEG 600 in 10 ml water was introduced into the segment. The catheter was then withdrawn

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and the oral ligatures were tied. Care was taken to avoid spilling PEG into the abdomen. After deposition the operation was arrested for 20 minutes and the planned resection, including the isolated ileal segment, was then carried out. Previous pilot tests had shown that 10 ml fluid could easily be introduced into a 15 cm segment of ileum without causing distension, even in the presence of chronic ileal inflammation.

The time from deposition of PEG to completed resection was similar in both patient groups. Thus the time range of exposure to PEG was 40–150 (mean 75) minutes in the Crohn's group and 45–119 (75) minutes in the colon carcinoma group. The urinary output was collected for six hours from the time of PEG deposition. The urine was frozen at -20°C and subsequently analysed for content of PEG. The methods for extraction and analysis of PEG were previously described.⁶

STATISTICAL ANALYSIS

Results are expressed as mean (SE) of the mean. The Wilcoxon's rank sum test, corrected for ties, was used for statistical evaluation, with $p < 0.05$ accepted as significant.

Results

The urinary recovery of the different sized PEGs is summarised in Table 1 and the Figure. In some cases no PEG, in particular of the larger sizes, was detectable in the urine. To avoid falsely low means, and to permit statistical evaluation, nondetectable PEG was coded as 0.05% , which was the lowest measurable value for absorption of any PEG.

The patients with colon carcinoma had little urinary excretion of all tested PEG sizes, and also

Figure Absorption molecular weight profiles for different sized PEG (590-942 dalton) in patients with colon carcinoma (left) or Crohn's disease (right). Per cent absorption of each molecular weight component was assessed from the urinary recovery over six hours following deposition of 4 g PEG 600 in an isolated ileal segment. Vertical lines indicate standard error of the mean.

showed decreasing excretion with rising molecular weight of PEG.

In Crohn's disease, the mean urinary excretion of PEG was always greater than in the carcinoma patients, and showed little variation according to molecular weight. The intergroup differences in PEG absorption were significant in the 678-942 dalton range.

There were no differences in six hour urine volume between the two groups, Crohn patients excreted 391

Table 1 Urinary recovery of different-sized PEG after ileal load in patients with colon carcinoma or Crohn's disease.

Molecular weight (dalton)	Urinary 6-hour recovery (% dose), mean (SE)		
	Colon carcinoma Patients (n=7)	Crohn's disease Patients (n=11)	Significance of difference (2-tailed p values)
590	0.45 (0.05)	1.28 (0.37)	>0.05
634	0.40 (0.10)	1.08 (0.43)	>0.05
678	0.38 (0.22)	1.33 (0.52)	<0.01
722	0.12 (0.02) [2]	1.20 (0.51)	<0.001
766	0.10 (0.02) [3]	1.16 (0.59)	<0.001
810	0.10 (0.03) [4]	1.11 (0.60)	<0.001
854	0.08 (0.02) [5]	1.23 (0.62)	<0.001
898	0.06 (0.01) [5]	1.17 (0.69) [1]	<0.01
942	0.05 (0.00) [7]	1.20 (0.61) [2]	<0.01

Figures in square brackets denote number of patients with no ($<0.05\%$ of given dose) recovery of relevant size.

Table 2 Ileal permeability indices in patients with colon carcinoma or Crohn's disease

Molecular weight ratio	Permeability indices, means (SE)		
	Colon carcinoma Patients (n=7)	Crohn's disease Patients (n=11)	Significance of difference (2-tailed p values)
634/590	0.92 (0.22)	0.90 (0.13)	>0.05
678/590	0.84 (0.43)	0.96 (0.12)	<0.05
722/590	0.31 (0.08)	0.89 (0.12)	<0.01
766/590	0.26 (0.08)	0.94 (0.16)	<0.01
810/590	0.26 (0.09)	0.86 (0.18)	<0.01
854/590	0.23 (0.10)	0.90 (0.17)	<0.01
898/590	0.16 (0.04)	0.76 (0.17)	<0.01
942/590	0.12 (0.01)	0.75 (0.18)	<0.01

Calculated from data in Table 1 (permeability for individual PEG sizes/ value for PEG 590).

(228) ml and patients with colon carcinoma 656 (317) ml, $p > 0.05$.

Permeability indices, for evaluating mucosal selectivity to different-sized molecules, were constructed by dividing the absorption values for the various PEG weights 634-942 by the value for PEG 590. The ratios thereby obtained (Table 2) were generally higher in Crohn's disease than in colon carcinoma.

Discussion

Most investigations of gastrointestinal permeability in man are performed after the subjects have ingested various probe molecules. Discordance of results then probably depends on differing routes of uptake for different test substances.⁷ It is nevertheless likely that such tests predominantly reflect absorption in the proximal part of the small intestine, where permeability is much greater than in the distal part.⁸⁻¹⁰

Patients with Crohn's disease were reported to have increased intestinal permeability to orally administered lactulose, but impaired absorption of mannitol.^{11,12} Uptake of radiolabelled Cr-EDTA was increased in Crohn's disease of the small intestine, but appeared to be unaffected in Crohn's colitis, whereas radiolabelled Tc-DPTA showed increased absorption in both types of involvement, with no difference between the two.^{13,14} In earlier investigations with ingested PEG, we found that patients with ileocaecal Crohn's disease had impaired absorption of both PEG 400 and PEG 1000, and also diminished selectivity of the intestinal mucosa against larger molecules.^{10,15,16} A recent report described increased intestinal permeability to oral PEG 400 in Crohn's disease patients and in their clinical healthy relatives.¹⁷

Investigations using peroral probe molecules thus do not reveal the site of absorption, inflamed or otherwise, in the intestine. Our method of measuring permeability intraoperatively, in an intestinal segment converted into a tied loop, circumvents this problem. To our knowledge, no previous investigator has clearly shown increased permeability in a well defined, inflamed segment of intestine in man.

Although the duration of exposure to probe molecules was relatively short, the absorption of almost all sizes was sufficient for identification in urine in the patients with Crohn's disease. In the patients with colon carcinoma, the PEG uptake in general was less and in regard to larger molecules it was frequently insufficient for detection in the urine. Despite the relatively small numbers of patients, we thus showed significantly increased permeability to PEG, in at any rate the 678-942 dalton range, in Crohn's disease as compared with colon carcinoma. We also confirmed

our earlier findings^{10,16} of diminished selectivity of the mucosal barrier in Crohn's disease, permitting larger molecules to be absorbed in amounts almost equaling the uptake of small ones. The intergroup differences in permeability indices were further indications of this mucosal alteration. Our findings accord with an investigation of exsorption of intravenous polyvinyl π pyrrolidone (mean molecular weight 33 000 dalton) into the lumen of an intubated, inflamed segment of small intestine in Crohn's disease, which showed increased exsorption and loss of selectivity of the mucosal barrier.¹⁸

Derangement of mucosal barrier function has been suggested as a prime factor in the development of chronic inflammatory bowel disease.¹⁴ A permeable mucosa would permit absorption of microbial and dietary antigen, and this could initiate an inflammatory reaction or perpetuate and potentiate an already existing inflammation. The increased permeability of small intestine in Crohn's disease showed in the present study could have been secondary to the inflammatory process and attributable to mucosal ulcerations. Micro-ulcerations, however, have been found in otherwise non-inflamed mucosa in patients with Crohn's disease.¹⁹ The possibility cannot be excluded that increased intestinal permeability is a primary event in Crohn's disease and an important factor in development of the inflammatory process.

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