Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis

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Abstract

Increased colonic wall thickness has been reported in patients exposed to large doses of high strength pancreatic enzyme preparations who did not develop fibrosing colonopathy. This has been interpreted as evidence for a spectrum of subclinical disease. The relation between sonographically measured colonic wall thickness and pancreatic enzyme preparation and dose was studied in 86 children with cystic fibrosis (CF). Colonic wall thickness of a control group was also measured. The average thickness in all colonic regions was higher in the CF group (overall average range 0.7–2.5 mm v 0.6–1.4 mm in the control group). There was no significant relation between colonic wall thickness and age, sex, total dose of lipase, or copolymer. Apart from one patient with an early colonic stricture, none of those exposed to high doses of lipase, or the methacrylic acid copolymer Eudragit L30 D55, showed evidence of subclinical damage to the colon. The reproducibility of the sonographic measurements was poor.

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In 1993, five children with cystic fibrosis (CF) were reported with what appeared to be meconium ileus equivalent, which did not respond to medical treatment, and four had thickening and strictures of the colon.¹ The characteristic appearance and histology of the resected colonic specimens is now termed fibrosing colonopathy (FC).

FC is essentially a pathological diagnosis, requiring full thickness biopsy of the bowel wall to demonstrate the characteristic severe submucosal thickening by mature fibrous tissue.²

The only major change in treatment which had preceded the discovery of FC had been the introduction of high strength pancreatic enzymes (Pancrease HL (Cilag UK), Creon 25 000 (Solvay UK), and Nutrizym 22 (Merck)) into the UK in 1992, and it was suggested that they might have a causative role. Therefore, an epidemiological study was performed and a case controlled study was subsequently undertaken.³ Fourteen cases of FC were identified among over 6000 UK CF patients. A nested control study using controls from the UK CF survey confirmed an association between FC and the use of high strength preparations, but not standard prepa-

rations. There was a brand difference: Pancrease HL and Nutrizym 22 were associated with FC but Creon 25 000 was not.³

This controlled study generated two main hypotheses as to the cause of FC. The first was that it was related to high doses of the pancreatic enzymes having an adverse effect on the colon; alternatively some other constituent was toxic to the colon—for example, the coating of the microtablets. The two preparations associated with FC in the UK (Pancrease HL (Cilag, High Wycombe, Bucks, UK) and Nutrizym 22 (Merck, West Drayton, Middx, UK) contained the methacrylic acid copolymer Eudragit L (Röhm, Darmstadt, Germany), which in high doses has a toxic effect on the gut of animals. This copolymer has been suggested as an important factor in causing FC.⁴ This suggestion was supported by the report of FC in two children taking high doses of Nutrizym GR, the only standard preparation to contain methacrylic acid copolymer.⁵ Detailed analysis of the type of preparation taken by children who subsequently developed FC supports the role of methacrylic acid copolymer as a contributing factor.⁶

The suggestion that there may be a subclinical spectrum of abnormality related to prior use of the high strength enzymes^{7 8} prompted our present study.

Method

SUBJECTS

Eighty six CF patients and 12 controls underwent colonic sonography. The cystic fibrosis group comprised 41 boys and 45 girls with a mean age of 9 years 7 months (range 13 months to 18 years), while the controls comprised seven boys and five girls with a mean age of 7 years 1 month (range 3 years 8 months to 12 years 3 months); none were known to have gastrointestinal illness.

All the CF patients had undergone at least two sweat tests with sodium and chloride concentrations over 60 mmol/l. All had been genotyped and 51 were homozygous for the DF508 mutation. Sixteen children had first presented with neonatal meconium ileus, 23 with chest symptoms, and 32 with symptoms of malabsorption. Nine had been diagnosed by neonatal screening and six were siblings of newly diagnosed patients. At the time of the study four patients were pancreatic sufficient, 81 were receiving the standard strength enzyme preparations Creon and Pancrease, and one was taking Creon 25 000.

Fifty of the patients had previously received high strength pancreatic enzyme (HSPE) treatment—22 with Pancrease HL, 26 with Creon 25 000, and two with Nutrizym 22.

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Table 1 Present enzyme doses used in the paediatric cystic fibrosis clinic in units of lipase/kg/day

Age (years)	n	Median	Mean	Maximum	Minimum	> 10000	> 15000	> 20000
0-5	35	9036	9972	21407	3113	16 (46%)	6 (17%)	2 (6%)
5-10	38	9393	10024	25397	2848	19 (50%)	5 (13%)	2 (5%)
10-15	44	7853	7458	16667	1564	10 (23%)	3 (7%)	0
> 15	22	5047	5047	12880	1339	3 (14%)	0	0

Table 2 Mean (range) regional colonic thickness in cystic fibrosis patients and controls

	Ascending	Transverse	Descending
Patients (n = 86)	1.2 (0.7-2.5)	1.2 (0.9-2.5)	1.2 (0.9-2.2)
Controls (n = 12)	1.0 (0.6-1.2)	1.1 (0.9-1.3)	1.1 (0.8-1.4)

Details of previous enzyme treatments were obtained from the CF unit database. The prescribed enzyme dose had been determined by control of symptoms and the results of faecal fat estimations (table 1).

ULTRASOUND EXAMINATIONS

All the patients were scanned by a single operator (WHR) who was unaware of each CF patient's enzyme intake. The only exclusions were occasional uncooperative young children and a child who had undergone a total colectomy; those with lesser resections were examined as far as these would allow.

The sonographic technique was based on criteria suggested by Kedar *et al*, with bowel wall thickness being measured between the echogenic luminal contents and the outer border of the echo poor muscle.⁹ Apart from a four hour fast before examination, there was no special preparation.

A Siemens Quantum machine fitted with an 8 mHz curvilinear transducer was used to examine the large bowel from the caecum to the distal descending colon. Nine separate

measurements were obtained of anterior wall thickness in transverse section and average values calculated for the ascending, transverse, and descending regions. A maximum single value for the colon as a whole was also noted, as was its location.

Attempts were made to measure the colon when relaxed, although peristalsis was not formally graded. All subjects were also examined for the presence of intraperitoneal free fluid.

Fifteen of the CF patients were re-examined one to 12 months later to monitor their progress and assess the reproducibility of the method.

Results

The posterior colonic wall was frequently obscured by bowel contents; for this reason, we assumed that the anterior mural thickness reflected that of the whole colon wall. Air in the stomach caused difficulty in examining the splenic flexure of some patients, although this could be overcome by the patients drinking clear fluid just before scanning in this region. In some patients, earlier colonic resections meant that localising measurements in the proximal large bowel were difficult to perform. No intra-abdominal free fluid was detected in any subject and no consistent change in colonic thickness was detected with age.

Average regional colonic thickness on initial examination of the CF patients and controls are listed in table 2. The controls had a significantly lower average thickness in all areas, derived from narrower ranges of values ($p < 0.01$ in all three areas of the colon; two sample *t* test).

Figure 1 Reproducibility of maximal colonic thickness between scans.

Figure 2 Plot of average ascending colon thickness against lipase use (units/kg).

Figure 3 Plot of average ascending colon thickness against copolymer use (mg/kg).

Figure 4 Comparison of distal ascending colon thickness and previous exposure to copolymer.

CF patients also had higher single maximum values for the colon as a whole (mean 1.6 mm, range 1.1–3.1 mm) compared to controls, none of whom exceeded 1.5 mm (mean 1.3 mm, range 1.0–1.5 mm).

In CF patients the maximum thickness involved the ascending colon alone in 22, the transverse colon in 16, and the descending colon in 28 patients. In 19 patients the highest value was measurable in two regions, and in one patient it was measurable in all three regions. The controls did not show a consistent maximum value in any particular area.

Fifteen CF patients were rescanned: eight showed a fall in their maximum colonic thickness, six a rise, and one remained the same. The mean difference in the maximum measurements between the two examinations was 0.4 mm, with the largest rises and falls both measuring 0.8 mm (fig 1). Additionally, the area of colon from which the maximum thickness was derived differed between the two scans in 10 of the 15 cases.

Multiple regression analysis showed no significant relations between the thickness of the ascending colon (average, proximal, mid, and distal regions) and the patient's age, sex, total dose of lipase (fig 2) or previous dose of copolymer (fig 3).

Comparison of the difference between ascending colonic thickness in CF patients never exposed to copolymer with those with previous exposure was not significant ($p = 0.057$).

Figure 5 Contrast enema showing loss of haustration and poor distensibility of the ascending colon.

There was, however, a tendency towards increased thickness in the distal ascending colon in the group of patients previously exposed to copolymer (fig 4), although this was largely caused by measurements in one patient who may have had an early colonic stricture. She presented at 7 years old with persistent abdominal pain and a mass in the right iliac fossa.¹⁰ A contrast examination showed loss of haustration and poor distensibility of the ascending colon (fig 5). Ultrasound of the patient's ascending colon showed increased thickness of the colonic wall (fig 6) compared to normal (fig 7). Previously this patient had received HSPE brands containing copolymer and at present she remains asymptomatic on standard Pancrease (total daily dose 6000 u/kg/day lipase). There was no difference in colonic thickness of the CF patients diagnosed by neonatal screening compared with the CF group as a whole. Additionally, the four patients who were pancreatic sufficient did not show any lesser colonic thickness than the CF group as a whole.

As all but one patient had returned to a standard preparation before the ultrasound study, it is possible that a reversible lesion could have resolved or improved.

Figure 6 Ultrasound of ascending colon shown in fig 5, showing increased thickness of colonic wall.

Figure 7 Ultrasound of ascending colon showing normal thickness of colonic wall.

Discussion

A thickened gut in cystic fibrosis was described by Oppenheimer *et al* in 1975.¹¹ If bowel wall thickening is defined as any part of the colonic wall exceeding the maximum control value (1.5 mm), then 41% (35 of 86) of CF patients in our study demonstrated this compared with 51%⁷ and 81%¹² in previous studies. Measurements for the control group fell between the two studies quoted. The reported predilection for thickening of the proximal colon⁷ was not reproduced in our series. Similarly we did not demonstrate intraperitoneal free fluid in CF patients.

Unlike earlier series^{12, 13} we were not able to confirm an increase in colonic thickness with age.

McSweeney,⁷ Oades,⁸ and colleagues showed an association between colonic wall thickness and high dose of lipase, but HSPEs other than Creon 25 000 were disproportionately represented among patients with the most pronounced colonic thickening. In a subsequent study Haber *et al* found no such dose relation.¹² Data were not available, however, on which specific enzyme brands the CF patients were receiving, particularly whether they had received HSPEs containing copolymer. Also there were five asymptomatic patients with very thick colonic walls (more than 5 mm) to a degree described in FC¹ (three of them were taking more than 15 000 u/kg/day of lipase). Lucas *et al*¹³ did not show a relation between lipase dose and colonic wall thickness in patients receiving Creon 25 000. Pohl *et al* found a preponderance of HSPE preparations, in particular Panzytrat 40 000 (which contains copolymer), in patients with intestinal wall thickness of more than 2 mm.¹⁴ They reported that the highest values were in the caecum.

We found no significant relation between colonic wall thickness and total dose of lipase or copolymer, although there was a tendency towards increased thickness of the distal ascending colon in patients exposed to high doses of copolymer.

The different results between centres are unlikely to be caused by the sonographic approach, as there were only minor variations in technique, such as slightly different transducer frequencies. The discrepancies were possibly caused by different pancreatic enzyme regimens, although the proportion taking copolymer containing preparations is similar to that found in a previous study (50% *v* 54%).⁷ It is difficult to evaluate the results of the study by Haber *et al*,¹² as although a high proportion of patients were receiving high doses of HSPEs, no specific brands were related to colonic thickness.

The averaging of results for each region of the colon was designed to minimise the effects of inaccurate measurement, but results of the follow up scans in the CF patients showed that the method was poorly reproducible. However, the problems with the method mentioned earlier were regarded as constant between examinations so we consider them non-contributory. Although the interval between the first and second scans varied, this alone would not account for the varying results. Difficulty in measuring

exactly the same areas in exactly the same state of relaxation on the second scan were more likely to contribute to the measurement variability. None of the CF patients had a significant change of enzyme dose between the two scans.

This complication has resulted in more accurate monitoring of the gastrointestinal tract in CF patients, and earlier and more thorough investigation of persistent abdominal symptoms. Following advice on enzyme use from the Cystic Fibrosis Foundation, the Federal Drug Administration,¹⁵ and the UK Committee on Safety of Medicines¹⁶ no further cases of FC have been reported since June 1995. However, in 1997 a 15 month old boy who had been taking Nutrizym GR (equivalent to 15 000 units of lipase/kg/day) developed FC (R Nelson, personal communication). Enzyme doses have been reduced in many patients without adverse effects on absorption or nutrition.¹⁷

In 1994 our paediatric patients returned to one of the standard enzyme preparations, Creon or Pancrease, and are controlled on doses below or only slightly in excess of those recommended by the Committee on Safety of Medicines. However, all the clinical,³ experimental,² and pharmacological evidence⁶ indicates a dose related association with copolymer containing enzyme preparations and FC. We now avoid all preparations which contain copolymer in patients of any age.

In conclusion, this study confirms an increased colonic wall thickness in CF patients compared to healthy controls. We found no significant relation between colonic wall thickness and age, sex, and total dose of lipase or copolymer. Apart from one patient with a possible early colonic stricture, we found no evidence of subclinical disease in CF patients exposed to high doses of both lipase and copolymer. Even so, as FC has been associated only with enzyme preparations containing copolymer, we would not use these preparations (in UK, Pancrease HL, Nutrizym 22, and Nutrizym GR) in CF patients of any age.

In most CF patients malabsorption can be controlled with doses of enzymes within or only slightly in excess of those recommended by the Committee on Safety of Medicines, using either standard Creon or Pancrease, or Creon 25 000. The recently introduced Creon 10 000 is also free from copolymer.

The poor reproducibility of ultrasonic measurements of the colonic wall warrants a confirmatory contrast examination when strictures are suspected.

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