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Colonic strictures in children with cystic fibrosis on low-strength pancreatic enzymes.

Sir - Colonic strictures in children with cystic fibrosis were first reported in this journal. Although apparently related to the use of high-strength enteric-coated pancreatic enzymes, their precise aetiology remains uncertain. We describe this complication in a boy aged 9 months who had taken exclusively low-strength enzymes.

He presented at age 18 days with cough, loose stools, and weight loss, had raised serum immunoreactive trypsin, and was (F508 homozgous. He was commenced on Nutrizym GR (Merck) enzyme supplements (650 units protease, 10 000 lipase, 10 000 amylase per capsule of enteric-coated pellets) at three-quarters of a capsule with feeds (1140 units protease/kg daily). Because of suspected gastro-oesophageal reflux, cisapride 600(g four times daily and Gaviscon (Reckitt & Colman, UK) 1 sachet per feed were commenced. He also received intravenous antibiotics, inhaled corticosteroids and salbutamol and vitamin supplements, and was discharged home aged 6 weeks on prophylactic oral co-amoxiclav. On review aged 3 months Nutrizym GR was increased to one
and a half capsules per feed (1625 units protease/kg daily), and cisapride to 800 (g four times a day. Persistent loose stools prompted further increases in Nutrizym GR , which averaged 25 capsules daily by 6 months of age (2600 units protease/kg) and 30 capsules daily by 9 months of age (2925 units protease/kg). His weight remained below the third percentile, and he developed mild abdominal distension. At 6 moths of age, Carobel (carob seed flour; Cow & Gate, UK) was prescribed in view of constant regurgitation. His parents described his stool as remaining loose and fatty, and frequently containing unaltered pancreatic enzyme pellets. At 9 months he was admitted with a 4 day history of absolute constipation and increasing abdominal distention. A diagnosis of distal intestinal obstruction syndrome was made. Gastrographin enema (Schering, UK) and N-acetylcysteine by nasogastric tube produced some improvement, but when feeds were reintroduced signs of intestinal obstruction recurred. Bowel wall thickness would not be assessed by ultrasound examination but repeat Gastrografin enema demonstrated a long
stricture of the right hemicolon, which was confirmed by a laparotomy. A right hemicolectomy was done, the excised specimen showing narrowing of the colonic lumen to 0.3 cm with white fibrous thickening of the submucosa measuring 0.4 cm. Histologically there was dense fibrous tissue expansion of the submucosa of the caecum and ascending colon extending to the muscularis propria with serosal thickening. The mucosa was oedematous and the lamina propria contained some chronic infammatory
cells and eosinophils. There was focal atrophy of the muscularis mucosae. No vasculitis, fissuring ulcers, or granulomata were seen. The terminal ileal muscularis propria and serosa were mildly fibrotic but the submucosa was spared.

Noteworthy in this case is the young age of the patient, the use of only a low-strength enzyme formulation but in high doeage per kg body weight, and the coexistant administration of cisapride. The appearance of unchanged enzyme pellets in the stool, not uncommonly seen in young patients, indicates failure of dissolution of enteric coating in the small bowel, and is consistent with the parents' report that increases of enzyme failed to normalise the stool. This suggests the delivery of increasing numbers of intact pellets to the caecum and large bowel, perhaps exacerbated by cisapride, which shortens oracaecal transit time, although mouth to anus transit time was unaltered by cisapride in one study of children with cystic fibrosis. MacSweeny et al, with ultrasound examination, recently found an increased risk of colonic wall thickening in children taking high-strength enzymes which was doubled in those also taking laxatives. Our case refultes any suggestion that colonic strictures in cystic fibrosis can only result from high-strength pancreatic enzymes. It suggests that, as well as total protease or lipase dosage, the excessive delivery of intact enteric-coated pellets

to the colonic mucosa may be an important casual factor, although whether this might be a direct toxic affect, or due to the local release of enzymes, is unclear. Drugs that shorten orocaecal transit time might increase the risk and should be used with caution. Further guidance on the prevention of colonic stricture by appropriate formulation and dosage of pancreatic enzymes awaits the results of epidemiological and other studies. From Robert Jones, Katka Franklin, Richard Spicer, Jem Berry.

Sir - Fibrosing colonopathy (also known as strictures of the ascending colon) in cystic fibrosis patients was first descrobed by myself and my co-authors in 1994 (R.L. Smith, D. van Velzen, A.R. Smyth, D.A. Lloyd, D.P. Heaf. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes, Lancet 1995; 343: 85-86.) At the times we postulated a relation to the use of high-strength pancreatic enzymes which had been introduced to the market 12-15 months before presentation of the first child with this condition. In view of the reports of colonic strictures from our hospital and other cystic fibrosis centres in the UK and Denmark, the UK Committee on Safety of Medicines recommended in December, 1993, that, unless there were special
reasons, patients with cystic fibrosis should change to low-strength pancreatic enzyme preparations.

The last known case of fibrosing colonopathy in the UK associated with high-strength enzyme preparations was prepared in July, 1994. In the past month, however, I have reviewed the histopathology of two new severe cases in very young children (one was that of the 9-month-old described above). Both children had been treated with high doses of a low-strength enzyme preparation, Nutrizym GR. The possible link between the high-strength enzyme preparations Pancrease HL, Nutrizym 22, and Panzytrat 25000, previously found to be associated with the condition, and Nutrizym GR is that these products all have an enteric coating that includes methacrylic acid copolymer. Gastrointestinal toxicity, including subacute to chronic submucosal inflammation, submucosal oedema,
ulceration, and erosion have been reported in rates dosed with ethyl acrylate, a monomer contaminant of methacrylic acid copolymer. Since there has been no association found to date between fibrosing colonopathy and products such as Pancrease, Pancrex V, Creon, and Creon 25 000, which are not prepared with this coating material, it is feasible that methacrylic acid copolymer could be the key factor in the development of fibrosing colonopathy.

My concern is that we may have inadvertently continued to treat children with low-strength enzyme preparations coated with copolymer in the belief that they were safe even in high dosage. We may be facing a new epidemic of colonic strictures in small children who have been preferentially treated with Nutrizym GR because of its fine granular formation and ease of use in infant feeds.

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