Effect of misoprostol on fat malabsorption in cystic fibrosis

P J ROBINSON,* P D SLY,* AND A L SMITH†

Departments of *Thoracic Medicine and †Gastroenterology, Royal Children's Hospital, Melbourne, Australia

SUMMARY Misoprostol, a synthetic prostaglandin that is known to reduce gastric acid production and stimulate duodenal bicarbonate production, was evaluated in 22 patients with cystic fibrosis. In those patients who had greater than 10% fat malabsorption while taking pancrease the addition of misoprostol significantly reduced the degree of fat malabsorption.

The duodenal intraluminal environment in patients with cystic fibrosis differs from normal in several ways. (1) The concentration of pancreatic enzymes is appreciably reduced, in about 85% of patients, to such low levels that supplemental oral pancreatic enzymes are required to improve absorption of fat, protein, and carbohydrate.¹ (2) Bicarbonate deficiency, resulting also from pancreatic exocrine insufficiency, contributes to a duodenal pH lower than normal.² (3) Some patients may also have a hypersecretion of gastric acid.³ Excessively acidic duodenal pH would be expected to interfere with pancreatic supplement treatment by two separate mechanisms. Firstly, pancreatic enzymes are irreversibly degraded at a low pH—for example, lipase at pH <4.² Secondly, most pancreatic enzyme preparations in current use are enteric coated to protect the enzymes against a low pH such as that found in the stomach. The enzymes are not released from these protective coatings, however, until the pH is >5.5. In an excessively acidic duodenum both these factors would lead to a reduction in the amount of enzyme available. Agents which either increase bicarbonate secretion into the duodenum, or decrease gastric acid output, or both, would be expected to increase the amount of active enzyme available in the duodenum. This would be expected to reduce the degree of malabsorption.

Misoprostol is a synthetic prostaglandin of the PGE₂ class that is known to reduce directly gastric acid output and to stimulate bicarbonate secretion from the duodenal mucosa. This study was performed to see if the addition of misoprostol to routine pancreatic supplement treatment would improve absorption of ingested fat.

Patients and methods

Twenty two patients (18 boys, four girls) ranging in

age from 1.5 to 10.5 years (mean 4.4) were studied. All patients had been diagnosed as having cystic fibrosis with a sweat chloride concentration >60 mmol/l by pilocarpine iontophoresis. Two patients were withdrawn from the study because of protracted diarrhoea. We report the results of the 20 patients who completed the study.

The study consisted of two 14 day periods. During both periods subjects took their normal dose of pancrease. During one period misoprostol was added (100 µg every six hours). Subjects were randomised to take misoprostol during the first or second period. A three day faecal fat balance study was performed at the end of each 14 day period. Dietary recording was performed for four consecutive days and faecal collection was performed for the last three days of this period. Dietary fat input was calculated using the 'Microdiet' analysis program (Department of Mathematics and Statistics, University of Salford, United Kingdom). Where necessary the program was altered to include Australian foodstuffs.

Faecal fat estimation was calculated using the acid titration method of van de Kramer *et al.*⁴ The percentage of dietary fat malabsorbed was calculated by the equation:

$$\% \text{ Fat malabsorbed} = \frac{\text{Three day fat excretion (g)}}{3 \times \text{Mean daily fat intake (g)}}$$

Results

Results for two patients were not calculated because of incomplete dietary recording. Grouped data showed a significant reduction in fat malabsorption. Examination of the results, however, showed that only subjects with >10% malabsorption while taking pancrease (n=13) derived significant benefit from misoprostol. In this group, fat malabsorption fell from an average of 22% while on pancrease to 14% while on pancrease and misoprostol (p<0.002) (figure). Pancrease capsule intake did not vary significantly between the two 14 day periods (paired *t* test >0.05). Fat intake between the two study periods was significantly different (p<0.02) with the greater input being in the period when misoprostol was administered (77 g compared with 88 g). Six patients reported relief from chronic abdominal pain

Figure Comparison of fat malabsorption (as a percentage of ingested fat) in 13 patients taking pancrease and pancrease plus misoprostol.

while taking the misoprostol. These symptoms returned in five of these patients several days after misoprostol was stopped at the end of the study.

Discussion

The results of the present study have shown that misoprostol can further improve fat absorption in a group of patients with persistent fat malabsorption despite pancreatic supplements. In none of the patients studied, however, did the fat malabsorption return to normal. One possible explanation for this is that the dose of misoprostol was inadequate, there being no recommended paediatric dose of misoprostol currently available. For the purpose of this study the lowest dose effective in reducing acid output in

adults was used. It is also possible that this incomplete reversal of the fat malabsorption by misoprostol indicates that other factors in the small bowel are important in fat malabsorption in cystic fibrosis, such as biliary abnormalities and mucosal abnormalities of the small bowel.

Misoprostol is not appreciably absorbed from the gut and produces its actions by a direct effect on the bowel mucosa. Systemic side effects are therefore rare. The only side effects observed in the present study were of a local nature—for example, diarrhoea. The current adult experience of misoprostol has shown that a transient softening of bowel motions is sometimes seen on starting misoprostol (Searle, product information). The two patients who experienced noticeable softening of bowel motions experienced appreciable diarrhoea that did not subside after five days. These patients were withdrawn from the study and their diarrhoea subsided within 48 hours of stopping the misoprostol.

The increased fat input observed during the period of misoprostol administration may well reflect an improvement in appetite in these patients, many of whom suffer decreased appetite due to chronic abdominal pain. The resolution of this pain, as observed in some patients in this present study, may be the explanation for the improved dietary input of fat.

In summary this study has shown that the administration of misoprostol to patients with cystic fibrosis, who have residual fat malabsorption despite taking pancreatic supplements, produces a significant improvement in fat absorption.

The authors acknowledge the support of Searle Laboratories who donated the misoprostol for this study, and Mrs B Crawford who performed the faecal fat analysis.

References

- Wong LT, Turtle S, Davidson AG. Secretin pancreozymin stimulation test and confirmation of the diagnosis of cystic fibrosis. *Gut* 1982;23:744-55.
- Weber AM, Roy CC. Intraduodenal events in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1984;3 (suppl 1):S113-9.
- Cox KL, Isenberg JN, Ament ME. Gastric acid hypersecretion in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1982;1:559-65.
- van de Kramer JH, ten Bokkel Huiniak H, Weijers HA. Rapid method for determination of fat in feces. *J Biol Chem* 1949;177:347-55.

Correspondence and requests for reprints to Dr PJ Robinson, Department of Thoracic Medicine, Royal Children's Hospital, Melbourne, Victoria 3052, Australia.

Accepted 27 April 1988