Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome*

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SUMMARY Patients with the short bowel syndrome are usually afflicted by chronic diarrhoea and treated with opiate drugs, yet little documentation of the effects of such drugs on digestive function is available. In the present study we found that acute oral administration of loperamide resulted in 50% inhibition of postprandial trypsin and bilirubin output in patients with short bowel syndrome. These changes are consistent with an opiate effect.

The short bowel syndrome is characterised by malabsorption of many nutrients and malnutrition. Patients with short bowel are often treated with anti-diarrhoeal drugs which have an affinity for opiate receptors such as tincture of opium, codeine, diphenoxylate, and loperamide. Loperamide, a new synthetic anti-diarrhoeal drug related to diphenoxylate,1 has been shown to be clinically effective in reducing chronic diarrhoea and possibly improving digestive and absorptive function in the short bowel syndrome.2,3 Despite the widespread use of loperamide, there are no studies on the effects of the drug on postprandial secretory and motor activity of the gut. We report the influence of this drug on pancreatic and biliary secretion in patients with short bowels.

Methods

PATIENT SELECTION
Seven patients with short bowels and seven healthy age- and sex-matched controls between the ages of 27 and 79 years were studied. Criteria for selection of short bowel patients for study included small bowel resection of greater than or equal to 100 cm. Average length of resection was 164 cm and it involved only the distal small bowel. In three of the seven patients, the ileocaecal valve and a rim of ileum adjacent to the valve remained in place. Short bowel syndrome resulted because of resections for either Crohn's disease (five patients) or bowel infarction (two patients) secondary to ischaemia. Two of the patients were on home parenteral nutrition. Exclusion criteria included active Crohn's disease as determined by current barium studies and the surgeon's description of the remaining bowel at the last operation, a gastroenterostomy or other intestinal bypass procedures, pancreatic disease, and liver or biliary tract disease.

PROCEDURE
Each patient or normal control was intubated under fluoroscopic control after an overnight fast with a multilumen intestinal tube and a 14 French gastric tube. 3H-PEG in 0.15 m saline was perfused in the duodenum at the level of the ampulla of Vater at a rate of 2 ml per min. An aspiration site was located 20 cm distally at the ligament of Treitz.

After basal samples were obtained during a 30 minute period, the patient drank a 400 ml meal which consisted of a defined formula diet (Ensure) diluted 2:1 with water as it is frequently consumed by patients to make it iso-osmolar (300 mOsm). The distribution of nutrients was 14% protein (casein hydrolysates and soy protein), 31.5% fat (corn oil), and 54.5% carbohydrate (corn syrup solids and sucrose). 14C-PEG was mixed in the meal as the marker. Gastric and intestinal samples were obtained every 10 minutes after the meal until gastric emptying was completed (less than 5% of initial marker concentration in gastric sample). Samples were frozen for subsequent analysis.

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EXPERIMENTAL DESIGN
Each short bowel patient was studied on two consecutive days with random single blind administration of either loperamide (6 mg at five hours and at 30 minutes before the meal) or an equivalent placebo capsule. This dosage is consistent with that which may be used in patients with severe short bowel syndrome. Each normal control was studied on a single day with administration of placebo.

ANALYTICAL METHODS AND CALCULATIONS
Trypsin and bilirubin concentrations were determined in duodenal aspirates by methods previously used in this laboratory. $^{14}$C-PEG and $^3$H-PEG were measured in gastric and duodenal samples by dual-isotope β-scintillation counting (Beckman Instruments, Fullerton, Ca, USA). Outputs of trypsin and bilirubin and gastric emptying of the meal marker ($^{14}$C-PEG) were quantified by reference to $^3$H-PEG concentration in duodenal aspirates using formulas previously described in detail. $^4$ $^5$ We have previously shown, as well, that duodenal flow can be accurately measured during gastric emptying of a meal, despite rapid variations in flow rates. $^6$ Our duodenal aspiration procedure, as opposed to fixed-volume sampling, closely approaches the ideal conditions of recovery proportional to intraluminal flow postulated by Levitt and Bond. $^7$ This method of quantifying postprandial pancreatic and biliary outputs has been successfully applied in previous studies by our group $^8$ and other investigators. $^9$ $^{10}$

Results
Trypsin and bilirubin outputs in patients with short bowels were not significantly different from control values at any time during the postprandial period. However, when patients with short bowels were given loperamide, a significant decrease in fasting and postprandial trypsin and bilirubin output occurred. As shown in Fig. 1, trypsin output in response to the meal was markedly decreased throughout the postprandial period. Trypsin concentration was also significantly reduced after loperamide (data not shown), thus indicating that a

Fig. 1 Postprandial trypsin output in short bowel patients: loperamide vs placebo. The asterisks indicate a significant ($P<0.05$) difference by the paired t test between patients given placebo and loperamide ($n=7$).

Fig. 2 Postprandial bilirubin output in short bowel patients: loperamide vs placebo. The asterisks indicate a significant ($P<0.05$) difference by the paired t test between patients given placebo and loperamide ($n=7$).
decreased secretion of the enzyme and not merely a decrease in pancreatic flow occurred. Although postprandial bilirubin output was also lower in the loperamide treated group, individual variability in bilirubin output resulted in fewer significant differences at 10 minute intervals (Fig. 2).

To correct for possible differences in gastric emptying rate, the data were also calculated as cumulative outputs from meal ingestion to the time that the stomach had emptied 95% of its contents. The difference between placebo and loperamide was significant (Table) with greater than 50% reduction in trypsin and bilirubin outputs after loperamide administration.

Table  Mean postprandial trypsin and bilirubin outputs* in healthy individuals and patients with short bowel syndrome on loperamide or placebo

<table>
<thead>
<tr>
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<th>Health (n=7)</th>
<th>Short bowel (n=7)</th>
<th>Loperamide</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
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<tr>
<td>Trypsin output</td>
<td>8.8 NS</td>
<td>6.4</td>
<td>2.6</td>
</tr>
<tr>
<td>(Ku)</td>
<td>±1.1 NS</td>
<td>±1.1</td>
<td>±0.4</td>
</tr>
<tr>
<td>Bilirubin output</td>
<td>8.6 NS</td>
<td>12.3</td>
<td>4.6</td>
</tr>
<tr>
<td>(mg)</td>
<td>±1.5 NS</td>
<td>±4.0</td>
<td>±0.7</td>
</tr>
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</table>

*Cumulative outputs measured from meal ingestion to the time that the stomach had emptied 95% of the meal. Values are means±SEM.

Discussion

The inhibitory effect of loperamide on pancreatic and biliary responses to food is consistent with an opiate effect. Opiate receptors are located, among other places, in the pancreas, duodenal mucosa, and cystic duct. Inhibition of pancreatic secretion by opiates has been demonstrated in dogs and rats. In dogs with pancreatic fistulae, morphine caused an inhibition of acid and exogenous secretin-induced bicarbonate and protein secretion. Although the effect of opiates on bile flow has not been studied extensively, gallbladder emptying has been inhibited by morphine administration in man. As loperamide lacks central opiate effects, we may conclude from our observations that peripheral opiate receptors may be involved in control of human pancreatic and biliary secretion.

Opiates increase duodenal muscle tone and inhibit propulsive motor activity. These effects in turn may cause partial obstruction of the sphincter of Oddi and increase pressures in the biliary and pancreatic ducts. It has been shown that flow of saline through the sphincter of Oddi is decreased after intravenous morphine. The depression of trypsin after loperamide in this study, however, cannot be explained by increased resistance at the sphincter of Oddi, as concentration as well as total output of trypsin were decreased.

Normal trypsin and bilirubin outputs in these short bowel patients were not unexpected. Although patients with extensive proximal small bowel resections may lose sites of secretin and cholecystokinin-pancreozymin (CCK-PZ) synthesis and hence have decreased pancreatic and biliary secretions, the patients in our study had primarily distal small bowel resection. Two of seven patients were on home parenteral nutrition; however, each was at his ideal body weight at the time of study and was taking food by mouth. Hence, pancreatic insufficiency secondary to the absence of intraluminal nutrition and prolonged parenteral nutrition or protein calorie malnutrition cannot explain our results.

Bilirubin serves as a marker of bile flow, which, like pancreatic secretion, should not be impaired after distal small bowel resection. Bile acids, on the other hand, may be decreased after resections greater than 100 cm of the distal small bowel. Bile acids were not used to determine biliary secretion, as a low value could have reflected a decrease in pool size because of intestinal losses and/or a decrease in biliary flow.

The implication of loperamide's effect on pancreatic and biliary secretion is potentially important. In patients being treated for diarrhoea, a reduction in biliary and pancreatic output is undesirable. In patients with normal pancreatic function, the reduction in enzyme output by loperamide is probably not significant, as enzyme output must be reduced to less than 10% before steatorrhoea and creotorrhoea due to pancreatic insufficiency appear. However, such severely malnourished patients in whom loperamide would be used probably have depressed pancreatic function on the basis of malnutrition which will be compounded by the use of loperamide. A reduction in bile output is of obvious concern in patients with short bowels who, if they have lost more than 100 cm of the distal bowel, may have a deficiency of bile acids.

References

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