Postprandial gastric function in pancreatic insufficiency¹

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SUMMARY Abnormalities in postprandial gastric function could contribute to the maldigestion of pancreatic insufficiency. To measure simultaneously postprandial gastric secretion and emptying and correlate these measurements with intraluminal duodenal changes, we performed intestinal intubation and duodenal perfusion during feeding of a solid-liquid test meal in 10 healthy controls and 10 patients with documented pancreatic insufficiency before and after replacement therapy. In pancreatic insufficiency, intraduodenal pH was significantly decreased late in the postprandial period while simultaneously measured duodenal acid loads were normal, confirming that reduced bicarbonate output rather than increased acid delivery was responsible for higher duodenal acidity in these patients. Significant ($P < 0.05$) reductions in postprandial acid, pepsin, and total secretory outputs were noted in untreated patients only during the first postprandial hour. Absolute gastric emptying rates were lower in patients ($P < 0.05$) than in healthy subjects, but fractional rates of emptying were similar. Fasting and postprandial hypergastrinaemia were consistently observed in the patients with pancreatic disease. There are postprandial disturbances of secretory function but no primary gastric motor defect in patients with exocrine pancreatic insufficiency.

Relatively little is known about postprandial disturbances of gastric secretory function and motor activity in patients with pancreatic insufficiency. Basal and histamine-stimulated acid outputs are often decreased in chronic pancreatitis (Bank *et al.*, 1966; Chey *et al.*, 1968; Gupta and Rao, 1975; Kravetz and Spiro, 1965), presumably related to the presence of ethanol-induced gastritis, although some authors have noted normal gastric secretory responses to secretagogues (Saunders *et al.*, 1978). However, gastric acid secretion after meals has not been adequately studied. In these patients (DiMagno *et al.*, 1973, 1977), postprandial secretion of pancreatic enzymes and bicarbonate is greatly reduced and intraluminal digestion is impaired. Changes in

gastric secretory and motor function could adversely affect the already compromised intraluminal digestion through several mechanisms. First, acid delivery into the duodenum is dependent on both gastric secretion and emptying. Increased rates of acid delivery could contribute to the abnormally low duodenal pH observed in pancreatic insufficiency (DiMagno *et al.*, 1977) and could inactivate endogenous and exogenous hydrolytic enzymes. Second, more rapid emptying of postprandial gastric contents could further reduce the intraluminal concentrations of enzymes. Finally, alterations in the normal co-ordination between nutrient delivery into the duodenum and enzyme secretion could further impair hydrolysis.

Gastric emptying of liquid fat meals has been reported to be abnormally rapid in pancreatic insufficiency (Long and Weiss, 1974). However, in that study, only emptying of the liquid meal itself was measured and the potential influence of altered secretory rates was not considered.

Utilising methods previously developed and validated in our laboratory (Malagelada *et al.*, 1976), we simultaneously measured gastric secretion and emptying after a mixed solid-liquid test meal in

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patients with advanced chronic pancreatitis. The effect of standard therapy with oral pancreatic enzymes on gastric function was also studied.

Methods

PATIENTS

The study involved 10 patients with severe exocrine pancreatic insufficiency (defined as less than 10% of normal enzyme outputs in response to cholecystokinin and steatorrhea while on a 100 g fat diet) (DiMagno *et al.*, 1973) and 10 healthy controls. No subject had known coexisting gastroduodenal disease. The cause of the chronic pancreatitis was alcohol abuse in seven and was unknown in three. Six of the patients had diabetes mellitus, and four required daily insulin. The mean ages ($\pm$ SE) of the pancreatic insufficiency group was 57 ($\pm$ 2.1) compared with 47.5 ($\pm$ 4.4) for the healthy controls. Nine men and one woman were in each group. Informed, written consent was obtained from all subjects.

DESIGN OF PERFUSION STUDIES

All volunteers and patients underwent intubation and intestinal perfusion as previously described (Malagelada *et al.*, 1976). After an overnight fast, a single-lumen gastric tube and a double-lumen duodenal tube were fluoroscopically positioned. Normal saline containing ^{14}C -polyethylene glycol was perfused through an infusion port located at the ampulla of Vater, and duodenal contents were aspirated from a second site at the ligament of Treitz (Malagelada *et al.*, 1976). The gastric sump tube was positioned in the antrum.

During the first 60 minutes of each study, three samples were collected from the gastric and duodenal aspiration sites to assess basal secretory outputs. Subsequently, a solid-liquid test meal consisting of hamburger, ice cream, bread, butter, and water containing 15 g PEG was ingested (Malagelada *et al.*, 1976). Gastric and duodenal samples were obtained at 10 minute intervals thereafter for the duration of the study. Blood samples were drawn before each study and every 30 minutes during the study.

Three groups of meal studies were performed in (1) 10 healthy volunteers, (2) 10 patients with pancreatic insufficiency, and (3) eight of the same 10 patients with pancreatic disease who were given eight pancreatin tablets (Viokase, Viobin Corp.) with the meal (two tablets at the beginning and end and four throughout the meal).

Gastric samples were analysed for pH and concentrations of acid, pepsin, and PEG (Malagelada *et al.*, 1976). Calculation of volumes and secretory outputs was based on previous assumptions

(Malagelada *et al.*, 1976). Serum gastrin was measured by radioimmunoassay (Sizemore *et al.*, 1973).

STATISTICAL ANALYSIS

The rank-sum test was used to determine statistical significance.

Results

GASTRIC SECRETORY OUTPUTS AND GASTRIC PH

Patients with untreated pancreatic insufficiency produced significantly ($P < 0.05$) lower amounts of acid, pepsin, and total secretory volumes in the first postprandial hour (Fig. 1, Table). There was a delay in onset of the peak postprandial secretory output and a depression in the absolute values (Fig. 1). After treatment, peak secretory values were achieved more rapidly, but peak outputs were unchanged. Beyond the first hour, acid outputs and secretory volumes decreased and were similar in all groups tested.

The decreased secretion of acid during the first postprandial hour in pancreatic insufficiency was associated with early rises in intragastric pH, compared with the pH in health ($P < 0.05$) (Fig. 2). Corresponding changes in total intragastric titratable acidity (data not shown) were also observed.

VOLUME OF GASTRIC CONTENTS AND GASTRIC EMPTYING RATES

Patients with untreated exocrine insufficiency had

Fig. 1 Postprandial acid output in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

Table Hour postprandial outputs ($M \pm SE$) of acid and pepsin, secretory volumes, and acid emptied into duodenum in health and pancreatic insufficiency*

	Health		Pancreatic insufficiency			
	Hour 1	Hour 2	Without treatment		Plus pancreatin	
			Hour 1	Hour 2	Hour 1	Hour 2
Acid output (mmol)	43.1 $\pm$ 8.2	21.2 $\pm$ 2.2	22.9 $\pm$ 3.4*	23.2 $\pm$ 3.4	26.7 $\pm$ 6.3	21.7 $\pm$ 2.8
Acid emptied (mmol)	14.8 $\pm$ 4.3	23.3 $\pm$ 2.6	8.5 $\pm$ 1.3*	19.9 $\pm$ 3.7	13.2 $\pm$ 5.7	20.4 $\pm$ 4.5
Pepsin (mg)	331.9 $\pm$ 68.4	161.4 $\pm$ 13.4	231.8 $\pm$ 14.8*	222 $\pm$ 31.4	285.9 $\pm$ 35.1	235.8 $\pm$ 43
Secretion output (ml)	466.3 $\pm$ 41.4	209.4 $\pm$ 19.6	322.7 $\pm$ 41.7*	200.9 $\pm$ 29.2	335 $\pm$ 51.3	170.1 $\pm$ 35.3

*Significantly different from corresponding value in health ($P < 0.05$).

Fig. 2 Postprandial gastric pH in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

significantly lower gastric volumes throughout the postprandial period (Fig. 3). A delay and quantitative decrease in the absolute rate of emptying of gastric contents occurred during the first postprandial hour (Fig. 4). Thereafter, absolute emptying rates were similar to those observed in health.

Addition of exogenous enzymes tended to increase the volume of gastric contents toward normal, although the observed differences were not statistically significant (Fig. 3). The low absolute rates of gastric emptying were not affected by enzyme replacement (Fig. 4). Fractional rates of gastric

Fig. 3 Postprandial gastric volume in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

emptying (volume emptied into duodenum divided by gastric volume) were similar in all three groups (data not shown).

RATE OF DUODENAL ACID DELIVERY AND DUODENAL PH

The rate of acid delivery into the duodenum was significantly ($P < 0.05$) less in pancreatic insufficiency than in health (Fig. 5, Table). This deficit was again evident only during the first postprandial hour and was partially corrected by supplementary enzyme therapy.

Fig. 4 Postprandial gastric emptying in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

Fig. 6 Postprandial duodenal pH in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

Fig. 5 Postprandial rates of acid delivery into duodenum in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

Distal duodenal pH was below normal ($P < 0.05$) in treated and untreated patients with pancreatic disease (Fig. 6). Differences from health became evident approximately 90 minutes after ingestion of the meal.

Fig. 7 Postprandial serum gastrin in health (H) and pancreatic insufficiency (P). V = pancreatin (Viokase) treatment. * $P < 0.05$.

SERUM GASTRIN CONCENTRATIONS

Patients with pancreatic insufficiency exhibited fasting and postprandial hypergastrinaemia, which was not significantly altered by treatment with pancreatin (Fig. 7). However, no significant differ-

ences in the integrated gastrin response to a meal could be found. The hypergastrinaemia could not be correlated with differences in simultaneously measured gastric pH or intragastric hydrogen ion activity ($r = -0.27$, $P > 0.05$).

Discussion

In patients with advanced exocrine pancreatic insufficiency, we demonstrated decreased acid secretion in response to a solid meal, normal gastric motor function, and fasting and postprandial hypergastrinaemia.

The deficit in gastric secretion occurs only during the first hour after ingestion of the meal when gastric secretory outputs normally peak and is related to an early increase in gastric pH and decreased amounts of acid emptied into the duodenum. Thus, the relative hypochlorhydria previously noted in patients with alcoholic chronic pancreatitis in response to histamine stimulation also occurs in the postprandial state (Kravetz and Spiro, 1965; Bank *et al.*, 1966; Chey *et al.*, 1968; Gupta and Rao, 1975).

A reduced parietal cell mass likely is the basis for these changes. However, other factors, such as a diminished intestinal phase of acid secretion (due to impaired intraluminal hydrolysis of fat and protein secondary to a deficiency of pancreatic enzymes) (Clain *et al.*, 1977) and increased circulating levels of intestinal hormones with 'enterogastrone-like' effects (Johnson and Grossman, 1971) may also have a role.

In our studies, gastric motor function, measured as fractional gastric emptying, is similar in pancreatic insufficiency and in health. Although lower absolute rates of gastric emptying are observed in pancreatic insufficiency, this is caused by reduced gastric secretory outputs. An analogous situation is seen after administration of cimetidine, a potent antisecretory agent, to patients with duodenal ulcer. Absolute gastric emptying rates were decreased, whereas fractional emptying was unchanged (Longstreth *et al.*, 1977).

Long *et al.* (1974) described abnormally rapid gastric emptying of liquid fatty meals in pancreatic insufficiency, but, in their studies, only the rate of disappearance of the meal marker from the stomach was calculated and secretory outputs were not measured. Thus, faster evacuation of a meal less diluted by gastric juice (because of diminished gastric secretion) was interpreted as reflecting a primary disorder in gastric emptying when, in fact, it represents a normal adaptation to reduced total gastric volume. In patients with calcific pancreatitis, Knox and Mallinson noted a reduction in the expected slowing of gastric emptying in response to a meal of undigested triolein (Knox and Mallinson,

1970). However, no details of the technique used for the measurement of gastric emptying were given, and a similar reduction in secretion rates could be responsible for their results.

Fasting and postprandial hypergastrinaemia was observed in both treated and untreated pancreatic disease, but the integrated response to the meal was similar to that in health. These changes cannot totally be explained by differences in fasting acid secretion because basal acid outputs and simultaneously measured basal intragastric acidity were similar in all groups. However, a chronic reduction in postprandial gastric acidity might have resulted in hyperplasia of antral G-cells and hypergastrinaemia, as has been reported in other clinical situations (Hughes *et al.*, 1977; Stockbrugger *et al.*, 1977).

Previously, our group showed—and the present study confirms it—that there is a late postprandial decline in distal duodenal pH in patients with exocrine pancreatic insufficiency (DiMagno *et al.*, 1977). Others also have observed that these patients have a diminished capacity adequately to neutralise intraluminal acid (Dutta *et al.*, 1977). Because the amounts of acid secreted and emptied during the late postprandial periods were the same as in normal controls, this phenomenon undoubtedly reflects a diminished secretion of bicarbonate by the pancreas.

In summary, our studies have revealed distinctive postprandial disturbances of the secretory functions of the stomach in patients with advanced chronic pancreatitis. There is no alteration in the fractional emptying of gastric contents in pancreatic insufficiency and therefore no primary gastric motor abnormality. Fasting and postprandial hypergastrinaemia may be secondary to chronically reduced acid secretion. In the late postprandial periods, a normal rate of acid delivery into the distal duodenum, combined with a reduced capacity for intraluminal acid neutralisation, results in a large decrease in duodenal pH. Thus, our data further emphasise the importance of reducing gastric and duodenal acidity in pancreatic insufficiency in order to protect orally ingested pancreatic extracts and improve intraluminal digestion of fat and protein (Regan *et al.*, 1977, 1978).

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