Efficacy of Lower Than Standard Doses of Pancreatic Enzyme Supplementation Therapy During Acid Inhibition in Patients With Pancreatic Exocrine Insufficiency

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Goal: To compare, during strong acid inhibition with omeprazole, the effect of 2 different doses of an enteric-coated pancreatic enzyme preparation on fecal fat excretion and abdominal symptoms in patients with exocrine insufficiency due to chronic pancreatitis (CP).

Background: Treatment with pancreatic enzymes reduces fecal fat excretion in patients with CP but is rather unsuccessful due to irreversible lipase inactivation at pH below 4.

Study: Sixteen patients with CP (3 women, 13 men; age 53 ± 3 y) participated in this randomized double blind 2-way cross over study. Fecal fat excretion and fat intake were measured and abdominal symptoms (visual analog scales) were scored during a 2 weeks control period, during omeprazole 60 mg + pancreatic enzymes 10,000 Fédération Internationale Pharmaceutique IU lipase tid (treatment A) for 2 weeks and during omeprazole 60 mg + pancreatic enzymes, 20,000 Fédération Internationale Pharmaceutique IU lipase tid (treatment B) for 2 weeks.

Results: During acid inhibition with enzyme supplementation fecal fat excretion was significantly ($P < 0.01$) reduced compared with control: 18 ± 7 and 18 ± 5 g/24 h versus 36 ± 8 g/24 h for treatment A, B, and control, respectively. Abdominal symptom score and general well being improved significantly ($P < 0.05$) during treatments A and B versus control. No differences in fat excretion or symptoms scores between treatments A and B were observed.

Conclusions: During strong acid inhibition, lower than recommended oral doses of pancreatic enzymes are therapeutically effective with respect to fat absorption and symptom reduction.

Key Words: pancreatic exocrine insufficiency, enzyme supplementation, acid inhibition, steatorrhoea

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In patients with chronic pancreatitis (CP), exocrine insufficiency with maldigestion and malabsorption of lipids becomes manifest when pancreatic lipase output falls below 10%.[1] Treatment with pancreatin improves fecal fat excretion but does not restore absorption of lipids to normal because of irreversible inactivation of lipase at pH below 4.0.[2–5] Enteric-coated pancreatin miscrospheres[3,6,7] have the advantage of being protected against acid inactivation because the microspheres release enzymes when the enteric coat dissolves at higher pH in the duodenum or jejunum (usually at pH 5 to 5.5). Patients with CP have a lower intraduodenal pH compared with controls not only because of impaired pancreatic bicarbonate secretion but also from a higher gastric acid load to the duodenum due to gastric acid hypersecretion.[8,9] This acidic duodenal environment may impair the release of pancreatic enzymes from microspheres. Combining pancreatic microspheres with H_2 receptor antagonists or protonpump inhibitors has resulted in significant reductions in fecal fat excretion in patients with cystic fibrosis.[10,11] Little is known, however, about the clinical effect of combination therapy of pancreatic enzymes with acid inhibition in patients with CP. Bruno et al[12] have clearly shown that strong acid inhibition with omeprazole 60 mg daily, added to pancreatic enzymes substitution, significantly reduced fecal fat excretion compared with "pancreatin monotherapy" in patients with CP. Concerning the doses of pancreatic enzymes in enteric-coated microsphere preparation, at least 20,000 Fédération Internationale Pharmaceutique (FIP) IU lipase are advised to be taken with meals.[13] Higher doses further improve but do not normalize fat digestion. In patients with cystic fibrosis dose escalation of pancreatic enzymes from 10,000 to 20,000 FIP IU lipase with meals was effective only during acid inhibition and not during placebo.[10] Very high doses of pancreatic enzymes have been associated with fibrosing colonopathy in patients with cystic fibrosis.[14]

Aim of the present study was to compare, during strong acid inhibition with omeprazole, the effect of 2 different doses of enteric-coated pancreatic enzyme preparations on fecal fat excretion and abdominal symptoms in patients with exocrine insufficiency due to CP.

MATERIALS AND METHODS

Sixteen patients with CP (3 women, 13 men) with a mean age of 53 ± 3 y (range 27 to 74 y) participated in this randomized double blind single dummy study with 2-way cross-over design. The diagnosis of CP was based on clinical history and alterations in pancreatic morphology documented with computed tomography scan and endoscopic retrograde cholangio pancreaticography. The morphologic changes were scored according to the Cambridge classification.[15] In case of multiple data, the most severe score form computed tomography scan or endoscopic retrograde cholangio pancreaticograply was taken.

The interval between diagnosis of CP and the present study was 9 ± 2 y, range 4 to 20 y. Chronic pancreatitis was caused by alcohol in 9 patients, in 1 patient by pancreatic duct anomaly (pancreas divisum), and in 6 patients the cause was unknown (idiopathic). The Cambridge classification of the 16 patients revealed: "severe" in 12 patients, "moderate" in 3 patients, and "mild" in 1 patient. Calcifications were present in 12 patients and duct morphology was abnormal in 13 patients. In the 4 operated patients histology from peroperatively taken pancreatic biopsies revealed chronic inflammation and fibrosis compatible with CP. Four patients had previously undergone pancreatic surgery: a drainage procedure, the Partington-Rochelle pancreaticojejunostomy (n = 2), and duodenum preserving resection of the head of the pancreas (n = 2) for pain due to CP. Exocrine insufficiency, defined as fecal fat excretion > 10 g/24 h had to be present to enter the study. Impaired glucose tolerance was present in 6 patients, of whom 3 were insulin dependent. All patients were on pancreatic enzyme replacement therapy, with a mean of 4 ± 1 y. Eight patients used acid suppression: protonpump inhibition in 6 patients and H_2 receptor blockers in 2 patients. Pancreatic enzyme supplementation and acid suppression was stopped at least 3 days before the study. Informed consent was obtained from each individual and the protocol had been approved by the local ethics committee.

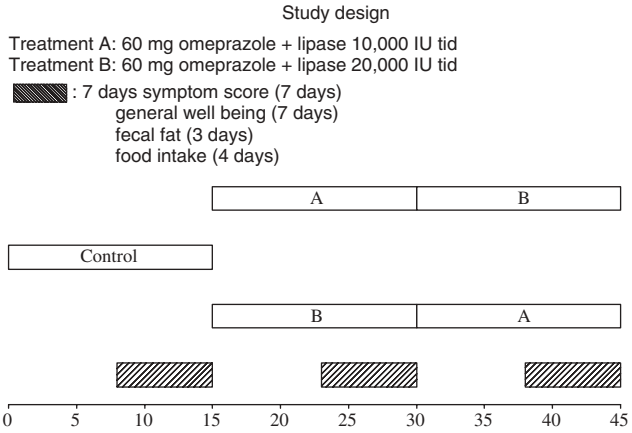

FIGURE 1. Study design.

Protocol

The study consisted of 3 identical 15-day period, (Fig. 1) First, a baseline period without pancreatic enzyme supplements or acid inhibitors. Thereafter in random order and crossover 2 treatment periods. Treatment A: omeprazole 60 mg with enteric-coated microspheres (Pancrease, 10,000 FIP IU lipase, tid) before meals and treatment B: omeprazole 60 mg with enteric-coated microspheres (Pancrease, 20,000 FIP IU lipase tid) before meals. Omeprazole 60 mg (3 capsules of 20 mg) was ingested 30 minutes before breakfast. Pancrease capsules during treatment A consisted of 2 capsules Pancrease (5000 FIP IU lipase, 2900 IU amylase and 330 FIP IU protease per capsule) together with 2 capsules Pancrease-placebo tid ingested just before meals. Treatment B consisted of omeprazole 60 mg and Pancrease 4 capsules tid ingested just before meals.

In the baseline period, after a run-in period of 7 days, abdominal symptoms and general well being were daily scored from day 8 to day 15 by visual analog scales with scores from 0 to 10 (0 = no symptom at all to 10 = intolerable). Abdominal symptoms asked for were: abdominal pain, cramps, bloating, and flatulence. General well being was also scored on a 10 point scale with 0 meaning "as bad as ever" and 10 meaning "never felt so good." From day 10 to day 14 food intake was noted in a diary to calculate daily caloric and fat intake. Stool was collected for 3 days from day 12 to 14 to determine fecal fat excretion and fecal elastase-1 concentration. The procedures were repeated during the 2 treatment periods.

Patients visited the outpatient department for instruction, stool collection and dispense of study medication at day 0 (start control period), day 15 (end of control period, start of treatment period 1), day 30 (end of treatment period 1, start of treatment period 2), and day 45 (end of treatment period 2). At each visit the study medication remaining from the previous 14 days was counted to assess compliance. A portion of ≥ 20% of medication not consumed (3 of the 15 d) was considered as noncompliance. Fecal fat excretion was measured according to the method of van de Kamer et al.[16] The coefficient of fat absorption was calculated by the formula:

$$\frac{\text{daily fat intake} - \text{fat excretion}}{\text{daily fat intake}} \times 100\%$$

Fecal elastase-1 was measured by a sensitive and specific enzyme-linked immunosorbent assay technique, described previously.[17,18]

Statistical Analysis

Results are expressed as mean ± SEM. Abdominal symptoms and scores for general well being are averaged over the 7-day period of data collection. Fecal fat excretion (g/24 h) and fecal elastase (μg/g) data were averaged over 3 days. Statistical analysis between the 2 treatments (primary aim) and between treatment and control period (secondary aim) were performed using Student *t* test for paired data in case of normal

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distribution or by Wilcoxon matched pairs signed rank sum test. The level of significance was set at $P < 0.05$.

RESULTS

Fecal Parameters

In the basal period fecal fat excretion was 36.5 ± 8.4 g/24 h and the fat absorption coefficient amounted 49 ± 8% (Table 1). Both treatments resulted in a significant ($P < 0.01$) reduction in fecal fat excretion to 17.9 ± 6.5 g/24 h during treatment A and 18.3 ± 4.7 g/24 h during treatment B. Fecal weight was lower during treatment A and B versus the basal period, but the differences were not significant ($P = 0.24$). During treatment A, the lower dose of lipase did not further increase fecal fat excretion compared with treatment period B with the standard dose of pancreatic enzymes. Food intake, especially fat intake, was comparable among the 3 study periods. Fecal elastase concentrations were significantly reduced in patients with CP (normal value ≥ 218 μg/g feces; 17) and were not affected by exogenous enzyme supplementation.

Symptoms

Abdominal symptom score was 3.2 ± 0.5 in the basal period and decreased significantly to 1.3 ± 0.3 during treatment A ($P < 0.01$) and to 1.2 ± 0.3 during treatment B ($P < 0.01$). General well being during the basal period was 4.9 ± 0.2 (0 to 10 point scale) and increased significantly to 6.1 ± 0.2 ($P < 0.05$) and 6.2 ± 0.2 ($P < 0.05$) during treatment A and B respectively. No differences in abdominal symptoms and general well being between treatments A and B were observed.

Clinical Parameters

The response to enzyme supplementation was not different between patients with alcoholic and idiopathic cause of the CP. Neither did previous pancreatic surgery affect outcome: basal fecal fat excretion was 33.8 ± 10.1 g/24 h in the operated patients (n = 4) versus 37.8 ± 9.5 g/24 h in the nonoperated patients. The response to treatments A and B in the 4 operated patients was in the range of the nonoperated patients. Fecal fat excretion decreased from 33.8 ± 10.1 to 16.3 ± 3.9 (treatment A) and 18.7 ± 4.1 (treatment B) in operated patients. Neither was the reduction in symptom score different between operated and nonoperated patients.

DISCUSSION

When in patients with CP, exocrine insufficiency becomes manifest by steatorrhoea or weight loss, pancreatic enzyme replacement therapy is indicated. It is usually recommended to ingest doses of 20,000 FIP IU lipase or higher with meals.[5,13] Enteric-coated pancreatin microspheres have the advantage over conventional enzyme preparations that they are protected against acid inactivation in the stomach. Although there is no strict linear relationship between the amount of lipase ingested and fecal fat excretion, increasing doses of enteric-coated enzyme preparations further reduce fecal fat excretion.[19] Combining enzyme therapy with drugs that inhibit gastric acid secretion further improves fat absorption.[3,6,7,11,12] These studies emphasize the influence of intraluminal pH on fat digestion because solubilization of fat and intraluminal pancreatic enzyme activity are both pH dependent.[20,21] Patients with CP have a significantly longer time with an acidic pH (pH < 5) in the duodenum compared with controls.[8]

Acid inhibitory drugs, especially protonpump inhibitors dose dependently increase intragastric pH.[21] After 40 mg omeprazole daily for 1 week, median 24 hour intragastric pH increases to 6.0 and with higher doses basal gastric acid secretion is almost completely inhibited.[22,23]

Our results demonstrate that during strong acid inhibition with 60 mg omeprazole daily, pancreatic enzyme supplements in a regular dose of 20,000 FIP IU lipase but also in a lower dose of 10,000 FIP IU lipase significantly reduces fecal fat excretion. Dose reduction to 10,000 FIP IU of lipase did not negatively affect on fat digestion and absorption. Differences in fecal fat excretion between treatment and control did not result from dietary factors because fat intake was comparable between the three study periods.

Pain is a classic and predominant symptom of CP. It has been hypothesized that during the course of long-standing CP pain decreases when exocrine and endocrine

TABLE 1. Effect of Dose Escalation of Pancreatic Enzymes During Acid Inhibition With Omeprazole on Fecal Weight, Elastase-1 Concentrations, Fecal Fat Excretion, and Fat Absorption in 16 Patients With Chronic Pancreatitis and Exocrine Insufficiency

		Treatment A	Treatment B
	Basal	Omeprazole + Lipase 10,000 IU tid	Omeprazole + Lipase 20,000 IU tid
Fecal fat excretion (g/24 h)	36.5 ± 8.4	17.9 ± 6.5*	18.3 ± 4.7*
Fecal elastase-1 (μg/g)	82 ± 46	56 ± 42	70 ± 50
Fecal weight (g/24 h)	396 ± 68	257 ± 38	293 ± 48
Oral fat intake (g/24 h)	72 ± 9	76 ± 7	76 ± 9
Fat absorption (%)	49 ± 8	76 ± 7*	75 ± 5*
Abdominal symptoms (0-10)	3.2 ± 0.5	1.3 ± 0.3*	1.2 ± 0.3*
General well being	4.9 ± 0.2	6.1 ± 0.2#	6.2 ± 0.2#

*$P < 0.01$, compared with basal.
#$P < 0.05$, compared with basal.

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pancreatic insufficiency become manifest. The patients we included in the study had a long interval between diagnosis and participation in the study. Exocrine insufficiency was present in all and pain was not predominant. Abdominal symptoms may well be related to malabsorption. Maldigestion and malabsorption of nutrients may provoke gastrointestinal symptoms such as diarrhea, abdominal cramps, bloating, and also pain. Abdominal discomfort negatively affects general well being and quality of life. Treatment of exocrine pancreatic insufficiency aims not only at increasing body weight and improving nutritional status but also at reducing abdominal discomfort and restoring the feeling of general well being. During therapy with omeprazole 60 mg daily combined with enteric-coated enzymes, abdominal symptoms decreased significantly and general well being improved significantly compared with the basal period. However, the regular dose of pancreatic enzymes did not affect symptoms or well being any further compared with the lower dose of enzymes. Therefore our results in patients with CP contrast with those obtained in patients with cystic fibrosis where dose escalation of pancreatic enzymes significantly improved fat absorption during omeprazole therapy.[10]

Several factors may be responsible for this difference in results. First, a type 2 error cannot be excluded because of large variation in fat excretion. Second, in the present study much higher doses of omeprazole were used (60 mg instead of 20 mg). Acid inhibition to pH > 5 improves the release of pancreatic enzymes from microspheres and prevents irreversible, pH dependent, lipase inactivation. With the strong acid inhibition we used, a dose of 10,000 FIP IU lipase tid already resulted in a 50% reduction in fecal fat excretion. Third, previous pancreatic surgery may affect the therapeutic response. Four of the patients we included had undergone pancreatic surgery (resection n = 2, drainage n = 2). However, neither basal fecal fat excretion nor the response to therapy were different among operated and nonoperated CP patients. Fourth, previous cholecystectomy may result in lower postprandial intraluminal bile acid concentrations. Low bile acid levels negatively affect fat solubilization and lipolysis. Basal fat excretion and the response to therapy were not different between the patients with (n = 3) and those without (n = 13) cholecystectomy. Fifth, patients with cystic fibrosis differ from CP patients with respect to exocrine insufficiency because fluid transport is diminished secondary to impaired chloride transport in cystic fibrosis. Patients with cystic fibrosis and residual pancreatic function have more benefit from adjuvant acid inhibition therapy than cystic fibrosis patients without or with minimal residual exocrine function.[24] This points to an additional therapeutic effect through an increase in bioavailability of endogenous lipase activity.

The patients with CP included in the present study had longstanding disease, with severe exocrine impairment demonstrated by high fecal fat excretion and low elastase output. Even though residual lipase activity is low, a small dose of 10,000 FIP IU lipase tid with meals significantly reduced fat excretion by 50%. Intraluminal lipase activity requires a minimum of 40 to 60 IU/min in chyme throughout the digestive period.[5] For a 2 to 3 hour postprandial period 10,000 IU of intraluminal lipase are sufficient. Acid inhibition will further reduce premature degradation of lipase in orally ingested pancreatic enzyme supplements. Ideally, all of the administered lipase contributes to intraduodenal and jejunal lipolytic activity.

In conclusion: during acid inhibition with 60 mg omeprazole, not only standard doses of 20,000 FIP IU lipase tid with meals but also lower doses of 10,000 of 10,000 FIP IU lipase significantly improve fat absorption by 50% and significantly and beneficially affect abdominal symptoms and general well being. No differences in efficacy between the 2 doses were observed. During conditions of strong acid inhibition even lower than recommended doses of pancreatic enzymes are therapeutically effective.

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