Fate of oral enzymes in pancreatic insufficiency

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Abstract

Oral pancreatic enzyme supplements, including those protected from gastric acidity by enteric coating, often achieve only partial correction of pancreatic steatorrhoea. To characterise the mechanisms involved in vivo, eight patients with steatorrhoea due to advanced pancreatic insufficiency and nine healthy controls were studied. Two sets of studies (small bowel intubation and five day faecal fat quantification) were randomly performed while patients were either on enteric coated pancreatin or equivalent placebo. A 260 cm long multilumen tube was used for double marker perfusion of two 20 cm segments located in the duodenum and in the ileum respectively. Luminal pH, flow, and trypsin and lipase activity outputs were measured at each segment for four hours postcibally.

Placebo treated patients with pancreatic steatorrhoea had low enzyme outputs in the duodenal test segment and even lower outputs in the ileal segment. Pancreatin treatment significantly decreased steatorrhoea ($p < 0.05$) and increased luminal enzyme outputs ($p < 0.05$). The increase was much greater in the ileal than in the duodenal segment. Thus enteric coated pancreatin treatment abolished the normal gradient between postcibal duodenal and ileal lipase output. The results suggest that enteric coated pancreatin nearly corrects severe pancreatic steatorrhoea. The ingested lipase was utilised inefficiently, however, as luminal enzyme activity in the ileum was enhanced to a greater extent than in the duodenum, and consequently the absorptive potential of the small bowel was only partially utilised.

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Patients with steatorrhoea due to advanced pancreatic insufficiency have extremely low duodenal pancreatic enzyme outputs (usually less than 5% of maximal output).¹ Oral replacement with pancreatic enzyme extracts (hereafter referred to as pancreatin) is a valuable form of treatment but complete abolition of steatorrhoea is not always achieved. Thus a number of approaches to improve the efficiency of enzyme replacement therapy have been investigated. These include lipase enrichment of pancreatin² and coadministration of H_2 blockers or omeprazole to prevent acid inactivation of enzymes (particularly lipase) and duodenal precipitation of non-ionised bile acids.³⁻⁶ Enteric coating of pancreatin into microspheres (1-2 mm) was also developed to protect enzymes from gastric acid without recourse to cotreatment with adjuvant medication.^{7,8} Full normal-

isation of fat absorption in every patient remains unachievable, however.

The precise reason why enteric coated enzyme preparations fail to perform as well in clinical practice as would be theoretically expected is an intriguing and important question. Delayed gastric emptying of the microspheres has been identified as a contributory factor⁹ but other factors may participate. Studies in healthy subjects indicate that pancreatic hydrolytic activity (and hence the potential for nutrient digestion and absorption) is present along the entire small bowel.^{10,11} Lipase activity in the distal ileum is low, however, suggesting that enteric conservation of lipase is precarious even under physiological conditions and that little of it is wasted into the colon.¹² The prevailing view is that interactions among lipase degradation by proteolytic enzymes, luminal mixing of chyme and secretions, and small bowel transit time probably determine the efficiency by which lipase secreted postcibally by the pancreas is utilised for optimal fat digestion and absorption in the human small bowel.

Our hypothesis was that patients with advanced pancreatic insufficiency, who are treated with enteric coated pancreatin, fail to optimally utilise it because the distribution of enzyme activity along the small bowel is caudally displaced by comparison with healthy subjects. Thus enzyme activity would be inappropriately low in the duodenum (where enteric coat dissolution should take place) and inappropriately high in the ileum (where enzyme wasting into the colon becomes inevitable).

Our aim was to test this hypothesis by measuring, by a multiple marker perfusion technique, postcibal pancreatic enzyme activity (concentration and output) at two extremes of the small bowel in patients with pancreatic steatorrhoea who were treated with either enteric coated pancreatin or with a placebo. Healthy volunteers were similarly studied to establish normal small bowel enzyme profiles under the conditions of the study.

Material and methods

PATIENT MATERIAL

We studied eight patients with steatorrhoea due to advanced pancreatic insufficiency and nine healthy controls. All patients (seven males and one female) had chronic alcoholic pancreatitis diagnosed clinically and confirmed in every patient by computed tomography scan and pancreatography. Moreover, all patients had abnormally low serum trypsin concentrations (range 20 to 100 ng/ml, normal > 140 ng/ml) and high faecal fat excretion (range 14.2 to 46.3 g/day, normal < 7 g/day). None were active

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alcoholic patients at the time of study. Six of the eight were diabetic patients requiring insulin.

Nine healthy volunteers (six males and three females) were also studied. Patients and volunteers gave written informed consent. The protocol for the study had been previously approved by our Institutional Review Board.

PROCEDURE

All patients underwent two different experimental procedures: perfusion studies and five day faecal fat balance studies. Healthy controls only underwent perfusion studies.

The perfusion studies were performed as follows. After an overnight fast participants were intubated under fluoroscopic control with a 260 cm long five lumen polyvinyl tube. Two of the lumens (outside diameter (OD) 1.0 mm, inside diameter (ID) 0.5 mm) were used for infusion and two others (OD 1.9 mm, ID 1.4 mm) for aspiration. The fifth channel had radiopaque walls and was connected to a small inflatable balloon at the tip of the tube. The aspiration ports were located near the tip of the tube and 130 cm proximal to it. The infusion ports were located 20 cm proximally to each of the aspiration ports.

Once the tip of the tube had advanced through the pylorus, the caudal balloon was inflated with 15 ml of air to facilitate progression of the tube along the small bowel. When it reached the distal ileum, the balloon was deflated and the position of the tube adjusted (by gentle withdrawal if necessary) so that the proximal perfusion port was in mid-duodenum just distal to the papilla of Vater. Participants then lay comfortably on a bed, head up about 45 degrees and the perfusion began.

Two saline solutions (0.15 M NaCl) were simultaneously infused at 5 ml/min via the proximal and distal ports. Phenol red (250 mg/l) was added as a non-absorbable marker to the duodenal perfusate and polyethylene glycol (4.000 (5 g/l) to the ileal perfusate. After a 30 minute equilibration period a standard test meal was fed to the participants while the perfusion continued for a further 4 hour period. The four hour duration of the study was established on the basis of previous studies^{10,13} showing that postcibal enzyme output had usually returned to baseline after such an interval.

The 500 ml liquid test meal contained 60 g of carbohydrates, 20 g of protein, and 20 g of lipids (Pentaset Standard, Nutricia, Zoetermeer, The Netherlands). Caloric proportions were 48, 16, and 36% respectively. The test meal was drunk by the participants within a 10 minute interval. Pancreatin or placebo capsules were administered with the meal. Pancreatin was administered as five capsules of a commercial enteric coated preparation. Each capsule contained 8.000 FIP lipase, 9.000 FIP amylase, and 450 FIP trypsin and chymotrypsin (Kreon, Kalichemie, Hannover, Germany), as verified in each batch of supplies.

Intestinal contents were recovered from both aspiration ports by siphoning aided by gentle suction when needed. Aspirates were pooled over ice at 30 minute intervals, care being taken

to remove no more than 10 ml during each interval to prevent depletion of chyme at the proximal port. From each of the nine pooled samples obtained from each site (one preprandial and eight postprandial) aliquots were separated for later analysis. All samples were stored at -20°C and assayed for lipase and trypsin within one to four days after the study. Under these conditions maximal loss of enzyme activity does not exceed 15%. All samples from each study were analysed on the same day.

The five day fat balance study was conducted as follows. Patients were admitted to the gastroenterology ward and fed a standard diet containing 100 g of fat per day. Stools were collected for two consecutive days after three full days on the fat diet. Stools were packed in sealed containers for later analysis.

In each patient two five day fat balance studies were randomly performed while they were receiving either pancreatin or placebo (five capsules with each of three daily meals).

ANALYTICAL PROCEDURES AND CALCULATIONS

Phenol red concentration was determined colorimetrically in duodenal samples and polyethylene glycol concentration in ileal samples.¹⁴ Marker concentration was also measured in the corresponding perfusates. pH was measured by a glass electrode in all intestinal aspirates. Trypsin and lipase activities were measured in all duodenal and ileal samples by titrimetric methods we have previously employed^{3,15,16} and expressed in Units. The conversion factor for each enzyme activity is as follows: 1 lipase Unit=5.3 FIP, 1 trypsin Unit=1 FIP. Faecal fat was measured by the standard gravimetric method¹⁷ and expressed as g fat excreted in stools per 24 hours.

Trypsin and lipase outputs per 30 minute period were calculated for the duodenal and ileal perfusion segments by the formula¹⁵:

$$\text{Enzyme output} = [\text{Enzy}_{\text{asp}}] \times \frac{[\text{Mark}_{\text{in}}] \times \text{Vol}_{\text{in}}}{[\text{Mark}_{\text{asp}}]}$$

where $[\text{Enzy}_{\text{asp}}]$ =enzyme (either trypsin or lipase) activity in the aspirate; $[\text{Mark}_{\text{in}}]$ =concentration of either polyethylene glycol or phenol

Figure 1: Cumulative postcibal trypsin outputs measured at the duodenal and ileal sites in healthy controls and in patients with pancreatic steatorrhoea with and without pancreatin treatment. Note logarithmic scale. See text for statistical analysis of these results.

Figure 2: Cumulative postcibal lipase outputs measured at the duodenal and ileal sites in healthy controls and in patients with pancreatic steatorrhoea with and without pancreatin treatment. Note logarithmic scale. See text for statistical analysis of these results.

red in the infusate; $[\text{Mark}_{\text{asp}}]$ = concentration of either polyethylene glycol or phenol red in the aspirate; Vol_{in} = volume of the marker solution perfused during each 30 minute interval.

STATISTICAL ANALYSIS

Trypsin and lipase outputs are expressed as means (standard error (SE) per period. Cumulative postprandial trypsin and lipase outputs were compared by calculating areas under each individual profile curve by the trapezoidal rule. Faecal fat excretion per 24 hours is expressed as mean (SE). pH data are expressed as median values (interquartiles).

Comparisons between groups were performed by the Student *t* test (paired for placebo *v* pancreatin and unpaired for patients *v* healthy controls). Comparisons between groups for pH data were performed by the Mann-Whitney U test.

Results

POSTCIBAL DUODENAL AND ILEAL OUTPUTS OF PANCREATIC ENZYMES IN HEALTHY SUBJECTS

In healthy subjects substantial amounts of enzymatic activity were present in the small bowel. Much higher outputs of both trypsin and

Figure 3: Postcibal luminal pH measured in samples from the duodenal and ileal sites in healthy controls and patients with pancreatic steatorrhoea with and without pancreatin treatment. Median values and upper interquartiles are presented. See text for statistical analysis of the results.

Figure 4: Faecal fat excretion measured by the 5 day standard fat balance in patients with pancreatic steatorrhoea with and without pancreatin treatment. Individual values are represented. The difference between placebo and pancreatin is statistically significant ($p < 0.01$).

lipase were measured, however, in the duodenum than in the distal ileum. For trypsin, the cumulative four hour duodenal output was about twofold greater than the ileal output ($p < 0.05$ (Fig 1)). For lipase, the duodenal output was five times higher than the corresponding ileal output ($p < 0.05$ (Fig 2)). The output profiles for both enzymes at each intestinal test site were similar suggesting that regional differences in enzyme output were consistent throughout the experimental observation period. Thus our results confirm that in normal subjects there is a significant loss of luminal enzymatic activity along the small bowel and that the magnitude of such loss is considerably greater for lipase than for trypsin.

POSTCIBAL DUODENAL AND ILEAL ENZYME OUTPUTS IN UNTREATED PATIENTS WITH PANCREATIC STEATORRHOEA

In placebo treated patients with pancreatic steatorrhoea extremely low postcibal outputs of trypsin and lipase activity were detected in the duodenum. Duodenal outputs were – as expected given the steatorrhoea that all patients presented¹ – well below 5% of equivalent outputs in healthy subjects, but some enzymatic activity was measurable in every patient.

In the distal ileum enzyme outputs were even lower than in the duodenum and, for lipase, activity became undetectable in six out of the eight patients; this suggests that, at least in these particular patients, whatever lipolytic capacity they were able to produce became exhausted as chyme progressed towards the caudad region of their small bowel. Ileal trypsin outputs represented about the same fraction of duodenal output, however, in patients with pancreatic insufficiency as in healthy controls (about 50% in both groups). Thus interestingly, the process of enzyme degradation along the small bowel (at least for trypsin) seems to be similar in severe hyposecretors and in healthy normosecretors.

POSTCIBAL DUODENAL AND ILEAL ENZYME OUTPUTS IN PATIENTS WITH PANCREATIC STEATORRHOEA TREATED WITH PANCREATIN

In pancreatin treated patients, duodenal trypsin and lipase outputs increased by comparison with placebo treatment. The increase was modest and in only two of the eight patients total duodenal outputs (exogenous plus endogenous enzyme activity) exceeded 5% of normal outputs (as determined in the healthy controls).

By contrast, in the distal ileum the increase in trypsin and lipase outputs in pancreatin treated patients was relatively much greater. Not only did it exceed by severalfold (more so in the case of lipase) the ileal outputs in placebo treated patients ($p < 0.05$) but pancreatin treatment also abolished the normal gradient between duodenal and ileal lipase output. That is, ileal lipase output became similar to duodenal output (Fig 2).

POSTCIBAL PH OF DUODENAL AND ILEAL CONTENTS

In healthy subjects, the pH of duodenal chyme fluctuated around 6–6.5 whereas ileal pH fluctuated at a significantly higher level around 7.5–8 ($p < 0.05$) (Fig 3). In placebo treated patients duodenal pH was slightly lower than in healthy controls. Median four hour postcibal chyme pH was below 6 in four out of eight patients with pancreatic insufficiency as opposed to only one in nine healthy controls. Ileal pH in both placebo and pancreatin treated patients was significantly higher than duodenal pH ($p < 0.05$) (Fig 3)). Ileal pH, by analogy with duodenal pH, was lower in patients with pancreatic insufficiency than in healthy controls ($p < 0.05$) suggesting that acidity of chyme in the patient group was abnormally high along the entire small bowel. Pancreatin treatment did not appreciably change pH either in the duodenum or in the ileum.

FAECAL FAT EXCRETION IN TREATED AND UNTREATED PATIENTS WITH PANCREATIC STEATORRHOEA

Placebo treated patients had an average daily faecal fat excretion of 30.2 (4.5) g (Fig 4). During pancreatin treatment faecal fat excretion fell to 11.6 (2.3) g/24 hours ($p < 0.01$). There was no apparent correlation between improvement in fat absorption during pancreatin treatment and duodenal or ileal lipase outputs, but the number of patients studied is small.

Discussion

We have shown that treatment of pancreatic steatorrhea with enteric coated pancreatin increases intestinal enzyme output and improves fat absorption. We have also found that this treatment does not fully reproduce the physiological match that occurs in normal subjects between the amount of luminal enzyme present in a given segment of small bowel and the length of intestine that remains available distal to that segment for digestion and absorption of nutrients. We believe that such an altered relation between enzyme activity and absorptive surface results in wasting of ingested enzyme and

contributes to an incomplete correction of the steatorrhea.

Lager *et al*¹² have shown that postcibal pancreatic enzyme output in healthy volunteers is maximal in the duodenal loop, gradually decreasing along the small bowel. Chyme nutrients are also progressively digested and absorbed. Whereas intraluminal trypsin specific activity remains constant throughout the small bowel, however,¹¹ the specific activity of lipase decreases rapidly due to its proteolytic degradation.^{18,19} Lipolytic activity is barely detectable in the distal ileum, the region where the absorptive capacity of the gut ends. Hence, lipase is a vulnerable enzyme that is conserved precariously even under physiological conditions.

In our present studies we have shown that patients with pancreatic steatorrhea have profoundly depressed duodenal enzyme outputs (as expected due to their exocrine insufficiency). Interestingly, however, these patients maintain a normal downward gradient of luminal enzymatic activity along the small bowel, at least for trypsin. Thus postcibal ileal trypsin output in our patient group amounted to about 50% of duodenal output, which is a similar proportion to that of the healthy controls. Because in pancreatic insufficiency lipase secretion is usually impaired to a greater extent than trypsin¹⁶ and, moreover, in our patients proteolytic activity was present along the entire small bowel, it was not altogether unexpected to find that in six out of our eight patients lipase activity had become totally exhausted before chyme reached the distal ileum. A key implication of such a finding is that patients with pancreatic steatorrhea fail to utilise the entire length of their small bowel for fat digestion and absorption. It follows that if more lipase could be delivered into the small bowel of these patients or if it could be protected better from proteolytic degradation there should still be intestinal surface reserve available for handling their usual dietary lipid load.

Enteric coated pancreatin partially achieves the goal of increasing intestinal enzyme activity as previously shown,²⁰ but in a somewhat inefficient manner, for reasons that become apparent from the analysis of our data. Firstly, we found that enteric coated pancreatin increased both duodenal and ileal enzyme output discretely and to a similar extent. Yet the duodenum receives a much higher nutrient load than the distal small bowel and duodenal chyme must still progress through most of the absorptive surface of the small bowel. It is, therefore, in the duodenum where most hydrolytic activity should be ideally present rather than in the ileum. Secondly, in pancreatin treated patients ileal enzyme activity turned out to be much higher than in placebo treated patients. Whereas such availability of luminal enzyme would seem to be in principle a favourable development, it is in fact a waste of enzyme because fat that becomes hydrolysed in the ileum has little absorptive surface ahead before chyme enters the colon. The waste of enzyme that should result from distal rather than proximal enzyme release acquires more severe consequences for lipase, an enzyme that is vulnerable and hard to conserve, than for trypsin or even amylase that are less

susceptible to intraluminal degradation. Thus we conclude that the lipase delivered into the intestine by the enteric coated preparation would have been used much more efficiently if it had been discharged into the duodenum than into the more distal small bowel.

The causes of the effects found are most likely related to the process of disintegration of the enteric coat. The coat is foremost designed to protect the packed enzymes from acid inactivation in the stomach and therefore it is pH sensitive with dissolution rates set to occur at pH 6 or higher. Yet, as shown by this and other studies,²¹ postcibal duodenal pH even in healthy subjects may remain below 6 for considerable periods. In patients with advanced pancreatic insufficiency, duodenal acidification is even more prominent due to, at least in the case of alcoholic patients,⁵ decreased pancreatic bicarbonate secretion rather than to gastric hypersecretion. In fact, in about half of our patients pH was below 6 for much of the postcibal period. It seems plausible that the enteric coat would not be immediately dissolved at the duodenal level. The gradual increase in pH that occurs as chyme moves caudally would make it dissolve later, but intestinal transit of solid particles in the postprandial period can be very fast. Like human lipase, porcine lipase is vulnerable to proteolytic degradation as shown *in vitro*.²² We cannot exclude the theoretical possibility that greater resistance of pig lipase to intraluminal proteolysis, compared with human lipase, would explain the increased ileal output in pancreatin treated patients. The fact that in three of eight patients ileal lipase output was higher than duodenal output suggests that a delayed opening of the enteric coat did occur, however, at least in those particular patients.

Delayed gastric emptying of large enteric coated particles containing pancreatin has been pointed out by Meyer *et al.*²³ The particles used in our study were 1–2 mm in diameter, slightly larger than the 1 mm size considered optimal by these investigators for concomitant emptying with the meal. It seems unlikely, however, that our results would have been determined by delayed gastric emptying of enteric coated pancreatin as, firstly, duodenal enzyme activities remained steady throughout the four hour postcibal period, a pattern similar to that found for emptying of solid nutrients.²⁴ Furthermore, based on data by Layer *et al.*¹² and findings from our own laboratory, beyond the fourth postcibal hour the test meal should have been completely emptied. Finally, ileal enzyme outputs were as high as duodenal outputs, a finding inconsistent with delayed gastric evacuation of pancreatin.

Our findings are highly relevant for the management of patients with advanced pancreatic insufficiency with oral enzyme replacement. This study shows that correction of steatorrhea is only partially achieved. The problem with enteric coated pancreatin seems to be not just a matter of how much lipase the patients actually receive but how much of it is utilised and where in the small bowel. If higher duodenal enzyme concentrations were obtained, fat hydrolysis would start more proximally in the small bowel. Then the available absorptive area would be

larger, ileal lipase concentrations would be lower, and hence lipase would not be wasted into the colon. These objectives could perhaps be achieved by a mixture of different enteric coat pH dissolution gradients to facilitate early duodenal release of a fraction of the ingested enzymes, or by other adjuvant procedures that deserve to be considered and explored in the future.

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