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Comparative effects of enteric-coated pancreatin microsphere therapy after conventional and pylorus-preserving pancreatoduodenectomy

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Background A comparative study was performed between patients with exocrine pancreatic insufficiency after conventional pancreatoduodenectomy (Whipple's procedure) and pylorus-preserving pancreatoduodenectomy (PPPD). In these patients the pharmacodynamics of 2-mm enteric-coated pancreatin microspheres (ECPMs) and their gastric transit time in relation to that of a solid meal were investigated. The efficacy of ECPM preparations may differ after Whipple's procedure compared with PPPD, because the latter procedure does not include gastrectomy.

Methods Gastric transit was assessed by double-isotope scintigraphy. A pancake meal was labelled with ^{99m}Tc. ECPMs were cold-labelled with ^{170}Er and neutron activated shortly before ingestion to enable imaging with a γ camera. Intraluminal pancreatic enzyme activity was assessed during a 6-h period with two indirect tests: the cholesteryl [^{14}C]octanoate breath test and the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid (NBT-PABA–PAS) test.

Results In patients who had Whipple's procedure, the gastric transit time of ECPMs and of the pancake meal was not significantly different. The outcome of the indirect pancreatic function tests during enzyme supplementation was comparable, and not significantly different, from that in healthy volunteers. In patients who had PPPD, however, the gastric transit time of microspheres was greatly delayed compared with that of the pancake meal ($P < 0{\cdot}05$). Improvement in the outcome of the indirect pancreatic function tests during enzyme supplementation was much less and remained well below that of healthy volunteers ($P < 0{\cdot}05$).

Conclusion In cases of exocrine pancreatic insufficiency after Whipple's procedure, 2-mm ECPM treatment adequately restores pancreatic enzyme activity. Following PPPD, however, ECPM treatment is often ineffective because the microspheres are retained in the stomach. In these patients, use of conventional powdered pancreatin enzyme preparations may improve the efficacy of treatment.

The prevalence of exocrine pancreatic insufficiency after pancreatic resection varies widely according to the type and extent of surgery, the selection of patients and the criteria set to define malabsorption[1–5]. Theoretically, it includes decreased activity of amylase, trypsin and lipase, producing carbohydrate, protein and fat maldigestion. In clinical practice, however, impaired digestion of fat is the key problem and the most difficult to abolish.

Exocrine pancreatic insufficiency has traditionally been treated with conventional (non-enteric-coated) pancreatin preparations. At present, enteric-coated pancreatin microsphere (ECPM) preparations are used with increasing frequency. These preparations consist of multiple pancreatin microspheres coated with a pH-sensitive polyacrylic acid surface. This layer dissolves if the gastrointestinal pH rises above a threshold (commonly 5·0–5·5) and offers partial protection against the fast and irreversible acidic inactivation of lipase (pH less than 4·0). Indications for postoperative pancreatic enzyme replacement therapy are determined by the consequences of exocrine pancreatic insufficiency: failure to maintain or regain body-weight due to high faecal caloric losses, and symptoms related to steatorrhoea such as frequent, loose and foul-smelling fatty stools, and abdominal cramps.

The classical conventional one-stage pancreatoduodenectomy includes cholecystectomy, resection of the distal common bile duct, duodenectomy, resection of the distal stomach, and excision of the pancreatic head and peripancreatic lymph nodes[6,7]. Reconstruction includes pancreatojejunostomy, hepatojejunostomy and gastroenterostomy. A major modification of Whipple's procedure was introduction of pylorus-preserving pancreatoduodenectomy (PPPD)[8,9]. The principal difference is the preservation of the stomach and 2 cm of the proximal duodenum and reconstruction by end-to-side duodenojejunostomy. Because of this, the efficacy of ECPM therapy after Whipple's procedure may differ from that following PPPD. The latter procedure has the advantage of preserving gastric capacity and gastric mixing ability, which may improve mixture of pancreatic enzymes and food. On the other hand, preservation of the stomach and pyloric function may also cause dys-synchronization in the gastric transit of microspheres and food, as was

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observed in healthy volunteers[10]. A comparative study was conducted between patients with exocrine pancreatic insufficiency after Whipple's procedure and after PPPD, to investigate the pharmacodynamics of ECPMs and their gastric transit time in relation to that of a solid meal.

Patients and methods

Experimental design

Patients ingested a solid test meal (pancake) together with 2-mm ECPMs (Panzytrat; Nordmark Arzneimittel, Uetersen, Germany). The gastric transit time of the pancake meal and the microspheres was determined, together with simultaneous assessment of intraluminal pancreatic enzyme activity by two indirect pancreatic function tests. Assessment was also performed without enzyme supplementation to determine endogenous pancreatic enzyme activity.

Patients

The study population consisted of seven patients who had undergone Whipple's procedure and five who had had PPPD. Resections were performed for malignancy of the pancreatic head region and included 80 per cent pancreatectomy with pancreatojejunostomy. All resections were done with curative intent. In two patients, one in each group, total pancreatectomy was performed. At the time of the investigation, no patient was known to have metastatic disease. Patients were selected for assessment of endogenous pancreatic function depending on complaints associated with maldigestion and steatorrhoea (abdominal pain, cramping, bloating, diarrhoea, foul-smelling stools) during postoperative follow-up. Patients were included in the study if the result of at least one of the two indirect pancreatic function tests was two standard deviations below the mean value for healthy normals.

The mean(s.d.) age of patients who had Whipple's procedure (six women and one man) was 66(5) years. The mean(s.d.) interval between investigation and surgery was 30(12) months. Underlying diseases were pancreatic adenocarcinoma (four patients), distal cholangiocarcinoma (one), villous adenoma of the duodenum (one) and leiomyosarcoma of the duodenum (one). After operation one patient developed insulin-dependent diabetes mellitus.

The mean(s.d.) age of patients who had PPPD (three women and two men) was 58(10) years. The mean interval between investigation and surgery was 12(4) months. Underlying diseases were pancreatic adenocarcinoma (four patients) and ampullary carcinoma (one). After operation two patients developed insulin-dependent diabetes mellitus.

A control group consisted of nine healthy men aged 21–30 years with no history of gastrointestinal, hepatic or renal disease, and with normal findings on physical examination[11].

The study was approved by the medical ethics committee. All participants gave written informed consent.

Assessment of gastric transit

Dual-isotope scintigraphy was used to assess the gastric transit profile of the 2-mm ECPM preparation in relation to that of the pancake meal. The pancake meal was labelled by incorporation of ^{99m}Tc-labelled albumin. For labelling the ECPM preparation, a technique involving cold labelling and post-production neutron activation was used. For this, part of the filler compound that was used to produce the ECPMs was replaced by ^{170}Er-enriched erbium oxide (Campro Scientific, Veenendaal, The Netherlands). Each microsphere of this batch contained approximately 0·3 mg ^{170}Er-enriched erbium oxide. Subsequent on-demand post-production neutron activation created the γ-emitting radioisotope ^{171}Er ($t_{1/2} = 7{\cdot}5$ h) and various radiocontaminants. Dosimetric criteria for optimum conditions for neutron activation had been established previously and it had been demonstrated that post-production neutron activation of ^{170}Er-enriched erbium oxide ECPMs could be performed safely within the guidelines set by the World Health Organization for experiments in human volunteers involving radioactive materials[12].

For each experiment, 50 ECPMs were neutron activated 8 h before ingestion, to yield 4 MBq ^{171}Er at the time of ingestion. The total committed dose equivalent, resulting from ingestion of the neutron-activated ECPM preparation, did not exceed 0·75 mSv per MBq ^{171}Er, including contributions from all contaminants. The effects of neutron irradiation on enzyme activity, gastric juice resistance and disintegration time of the ECPMs were acceptable, and permitted *in vivo* assessment of small intestinal enzyme activity during gastric transit studies[12].

All acquisitions were performed using a single-headed large-field-of-view camera (Diacam; Siemens, Dusseldorf, Germany) and the factory-standard high-energy collimator. For ^{99m}Tc a 15 per cent window centred at 140 keV and for ^{171}Er a 20 per cent window at 302 keV was used. Acquisitions were performed in dual-isotope mode and 64×64 pixel frames (16 bits per pixel) at a rate of one frame per 90 s. Individual frames were corrected for motion, downscatter, decay, background and attenuation. Calculation of gastric transit time was performed by means of location–time analysis, resulting in a transit time of the ingested activity quantifying the median delay between entrance into the stomach and passage through the pylorus[13,14]. Gastric transit time indicates the timepoint at which half of the ingested activity (i.e. pancake and ECPM) have left the stomach.

Assessment of pancreatic enzyme activity

Cholesteryl [^{14}C]octanoate breath test. The cholesteryl [^{14}C]octanoate breath test is based on the intraluminal hydrolysis of cholesteryl [1-^{14}C]octanoate by cholesterol esterase (carboxyl ester lipase); measurements of [^{14}C]carbon dioxide recovery in breath provide a non-invasive test for ester lipid hydrolysis[11,15]. Cholesteryl octanoate (unlabelled) was purchased from Sigma Chemical (St Louis, Missouri, USA). Cholesteryl [1-^{14}C]octanoate was synthesized at the University of California, San Diego, from [1-^{14}C]octanoic acid (New England Nuclear, Boston, Massachusetts, USA). Breath samples were collected by blowing alveolar air into a solution of 2 ml 96 per cent ethanol and 2 ml hyamine hydroxide 1 mol/l in methanol (Packard, Groningen, The Netherlands). Thymolphthalein (Fluka Chemie, Buchs, Germany) indicator was used to detect completion of saturation of hyamine hydroxide by 2 mmol expired carbon dioxide. [^{14}C]carbon dioxide output in breath was measured by liquid scintillation counting. Results were expressed as the percentage of administered radioactivity (^{14}C) excreted per millimole of carbon dioxide after correction for body-weight.

*N-benzoyl-L-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid test.* This test is based on the intraluminal hydrolysis of the peptide *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (NBT-PABA) by pancreatic chymotrypsin; measurement of plasma PABA concentrations or urinary PABA recovery provided an indirect test for protein digestion[11,16]. Calculation of the PABA:*p*-aminosalicylic acid (PAS) ratio corrects for possible defects in the absorption or alterations in postabsorptive metabolism of PABA[17]. NBT-PABA (sodium salt) was purchased from Fluka Chemie. PAS was purchased from Sigma Chemical. Concentrations of PABA in plasma (mg/l) were determined by high-performance liquid chromatography (HPLC), as were the concentrations of PABA and PAS in urine. Cumulative 6-h urinary recovery of PABA and PAS was expressed as the percentage of the amount of substrate recovered in the 6-h urine collection compared with the total amount administered orally. HPLC assays of PABA and PAS were performed as described elsewhere[11].

Test meal

The test meal consisted of a pancake made from 100 ml whole milk, 50 g flour and 25 g beaten egg. Cholesteryl [^{14}C]octanoate (5 μCi dissolved in 0·2 ml *n*-hexane) was mixed carefully into the

pancake batter together with 1·5 g cholesteryl octanoate. To this batter 15 MBq ^{99m}Tc-labelled albumin colloid was added. The pancake was fried in 10 g butter and spread with jam. Finally, 1000 mg NBT-PABA and 500 mg PAS were sprinkled on to the pancake. The meal contained 1527 kJ (365 kcal) and its calculated waterfree composition was 50 per cent carbohydrate, 37 per cent fat and 13 per cent protein.

Test procedure

Pancreatic enzyme activity was measured on two separate occasions in each patient. First, endogenous pancreatic enzyme activity was assessed. Second, pancreatic enzyme activity during enzyme supplementation was measured. During the latter procedure the gastric transit time of the 2-mm ECPM preparation and the pancake meal was assessed simultaneously. Five days before each test procedure, patients discontinued the use of pancreatic enzyme supplements and drugs that influence gastrointestinal pH (e.g. H_2-receptor antagonists, proton pump inhibitors) and motility (e.g. domperidone).

Participants fasted overnight. Before the test, fasting-state breath and blood samples were obtained for baseline determinations of [^{14}C]carbon dioxide output in breath and of plasma PABA concentration. An untimed urine sample was obtained for baseline urinary PABA and PAS excretion. During dual-isotope image acquisition, patients were seated in an upright position. First, a static image (180 s, frontal view) was obtained after the ingestion of two crushed ^{171}Er-labelled microspheres. This acquisition was used to calculate downscatter from the ^{171}Er channel into the ^{99m}Tc channel. The dynamic image acquisition (frontal view, maximal 130 frames, each of 90 s duration) was then started and patients were fed the pancake meal. Halfway, 50 neutron-activated ECPMs and 60 non-activated microspheres were ingested, without the gelatin capsule in which they are normally contained. Although not formally studied, it is believed that this ensures a better mixture of enzymes and food after antrectomy. For reasons of comparison, the same procedure was used in patients who underwent PPPD. The total enzyme dose was approximately 42000 units of lipase, 2250 units of proteases and 38000 units of amylase. Subjects ate the complete pancake. During ingestion of the pancake meal, they also drank 75 ml water. Following the dynamic acquisition, a static image acquisition (300 s, left lateral view) was obtained to visualize the body contour in relation to the position of the stomach and small intestine. This frame was used to compute the regional attenuation. From the start of ingestion of the pancake meal, breath and blood samples were collected at 30-min intervals for 4 h and then hourly for a further 2 h; urine was collected for 6 h. During the first 3 h after the pancake meal, patients were not allowed additional fluids. For 3–6 h, they were encouraged to drink at least 500 ml water or tea. Some 4 h after the pancake meal, they received a standardized light lunch.

Statistical analysis

Results are expressed as mean(s.d.). Data were compared with analysis of variance (ANOVA) (with correction according to Bonferroni for multiple testing) and Wilcoxon matched-pairs signed rank test. To calculate the area under the curve (AUC), for both [^{14}C]carbon dioxide output in breath and plasma PABA concentration, linear interpolation was used. Differences were considered significant when P was less than 0·05 for a two-tailed test.

Results

Gastric transit

Fig. 1 shows the gastric transit of the 2-mm ECPMS and the pancake after Whipple's procedure and after PPPD. After Whipple's procedure, the gastric transit time of the microspheres was 79(59) min and that for the pancake meal was 53(31) min (P not significant, Wilcoxon test). Following PPPD, the transit time of the 2-mm ECPMs was 119(43) min and that of the pancake meal was 50(20) min ($P < 0·05$, Wilcoxon test).

Pancreatic enzyme activity

Cholesteryl [^{14}C]octanoate breath test. Fig. 2 shows the results of the cholesteryl [^{14}C]octanoate breath test (AUC of 6-h [^{14}C]carbon dioxide output in breath) after Whipple's procedure and after PPPD, without and during enzyme supplementation. After Whipple's procedure, the mean AUC for [^{14}C]carbon dioxide output in breath rose to be no different from that of healthy volunteers. After PPPD, the mean AUC for [^{14}C]carbon dioxide output in breath rose from 15 per cent (without enzyme supplementation) to 57 per cent (during enzyme supplementation) of that of healthy volunteers. Outcome during enzyme supplementation remained significantly different from that in healthy volunteers ($P < 0·05$, ANOVA).

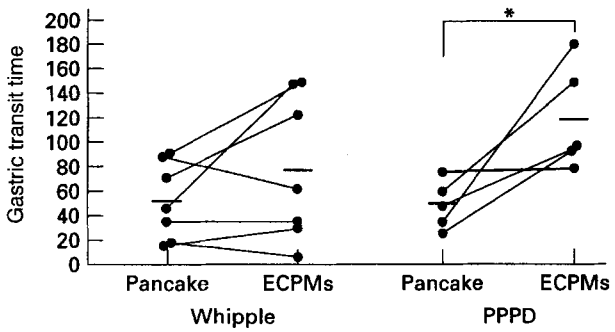

Fig. 1. Gastric transit time of the pancake meal and the enteric-coated pancreatin microspheres (ECPMs) after Whipple's procedure and after pylorus-preserving pancreatoduodenectomy (PPPD). Horizontal bars represent the mean. *$P < 0·05$ (Wilcoxon matched-pairs signed rank test)

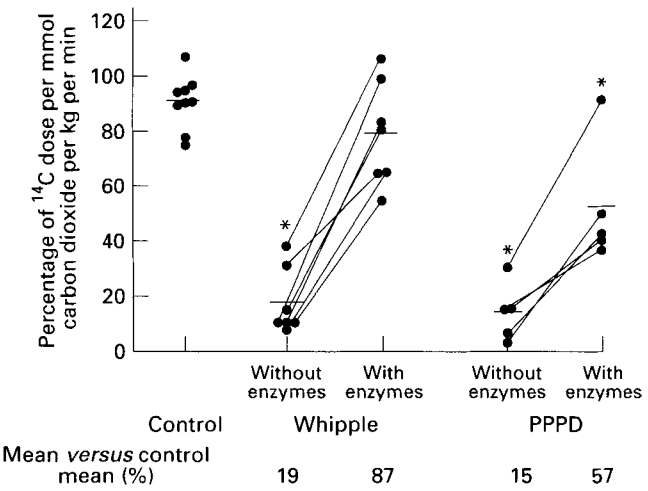

Fig. 2 Results of the cholesteryl [^{14}C]octanoate breath test (area under the curve) in nine healthy volunteers (control), in seven patients who had Whipple's procedure, and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation. Horizontal bars represent the mean. *$P < 0·05$ *versus* control (analysis of variance)

*N-benzoyl-L-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid test.* *Fig. 3* shows the results of the plasma PABA test (AUC of 6-h plasma PABA concentration) after Whipple's procedure or PPPD, without and during enzyme supplementation. There were no significant differences between patients who had Whipple's procedure (without and during enzyme supplementation), those who had PPPD (without and during enzyme supplementation) and healthy volunteers (ANOVA).

Fig. 4 shows the outcome of the 6-h urinary PABA:PAS ratio after Whipple's procedure or PPPD, without and during enzyme supplementation. The outcome during enzyme supplementation in those who had Whipple's procedure was not significantly different from that in healthy volunteers. In patients who had PPPD, the outcome during enzyme supplementation remained significantly different from that in healthy volunteers ($P < 0{\cdot}05$, ANOVA).

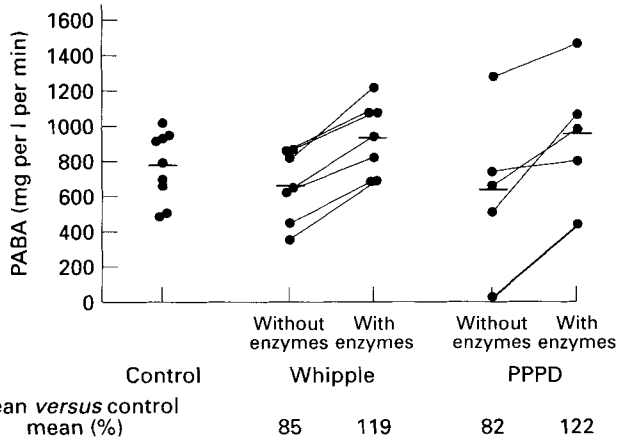

Fig. 3 Results of the plasma *p*-aminobenzoic acid (PABA) test (area under the curve) in nine healthy volunteers (control), in seven patients who had Whipple's procedure and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation. Horizontal bars represent the mean

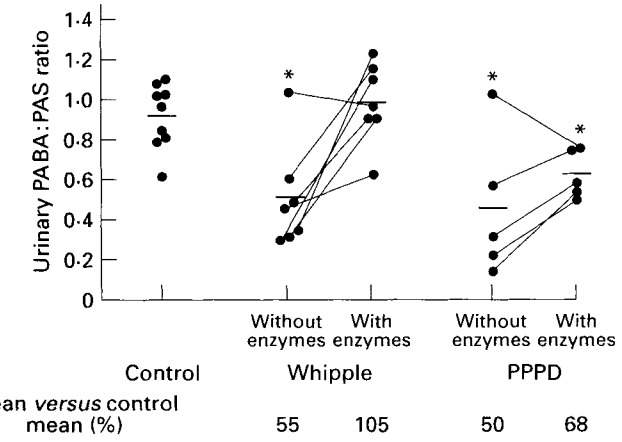

Fig. 4 Results of the urinary *p*-aminobenzoic acid (PABA):*p*-aminosalicylic acid (PAS) ratio in nine healthy volunteers (control), in seven patients who had Whipple's procedure, and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation. Horizontal bars represent the mean. *$P < 0{\cdot}05$ *versus* control (analysis of variance)

Discussion

The present study shows that after Whipple's procedure the gastric transit of ECPMs and food is synchronous and pancreatic enzyme activity is restored to normal levels, but after PPPD gastric transit of ECPMs is much delayed and pancreatic enzyme activity remains well below the normal level.

The essential modification of PPPD compared with Whipple's procedure is preservation of the stomach, which may entail a longer recovery time from delayed gastric emptying in the early postoperative period[18–20]. Whether exocrine pancreatic insufficiency develops after Whipple's procedure or PPPD depends on a number of factors, including the extent of the pancreatic resection, the quality and patency of the pancreatic anastomosis and the condition of the pancreatic remnant. In some patients with cancer of the pancreatic head this is already impaired before operation by fibrosis and atrophy of the parenchyma distal to the obstructing tumour. After pancreatic resection non-optimal stimulation of residual enzyme secretion and non-optimal mixture of enzymes, food and bile may contribute to impaired digestion of nutrients[21].

At present, no reliable data are available with respect to the prevalence of exocrine pancreatic insufficiency after Whipple's procedure or PPPD. If, however, exocrine pancreatic insufficiency has developed after operation, there may be a difference between these procedures with respect to the efficacy of pancreatic enzyme replacement therapy to restore digestive function. Preservation of the stomach has the advantage that the gastric capacity and gastric mixing ability are maintained, which may ensure a better gastric mixture of pancreatic enzymes and food. On the other hand, it may also cause ECPMs to pass through the stomach more slowly than solid food, as was observed in healthy volunteers[10]. In the volunteers, spheres with a diameter greater than 1·7 mm were retained in the stomach, compared with a solid meal.

The present study shows that, in patients who have had Whipple's procedure, the gastric transit time of 2-mm ECPMs is not significantly different from that of a pancake meal. This is in contrast to the results obtained in patients who have had PPPD, in whom the gastric transit of microspheres is much delayed compared with that of the pancake. This difference between the surgical procedures is also reflected in the intraluminal enzyme activity during enzyme supplementation, as measured by indirect pancreatic function test results which, at baseline, were comparable between both groups. During enzyme supplementation in patients who had had Whipple's procedure, results of the cholesteryl [^{14}C]octanoate breath test (reflecting intraluminal carboxyl ester lipase activity), the plasma PABA test (reflecting intraluminal chymotrypsin activity) and the urinary PABA–PAS test (reflecting intraluminal chymotrypsin activity with a correction for possible defects in the absorption or alterations in postabsorptive metabolism of PABA) were similar and not significantly different from those obtained in healthy volunteers. In patients who received enzyme supplementation after PPPD, however, much less improvement was observed, and the outcome of [^{14}C]carbon dioxide recovery in breath and the 6-h urinary PABA:PAS ratio remained well below those of healthy volunteers. Gastrointestinal pH was not measured as this might have interfered with the 'normal' physiology of digestive function in these patients. The possibility cannot,

therefore, be excluded that differences in the postoperative gastrointestinal pH profiles influenced the findings.

It must also be noted that the mean age of control subjects and patients differed. There are conflicting data on the effect of age on pancreatic exocrine function. However, if there is any decline in function with age, this is only marginal.

In conclusion, the results of this study show that preservation of the stomach in PPPD, compared with Whipple's procedure, impairs the synchronous release into the jejunum of ECPMs with solid food, thereby diminishing the efficacy of treatment. Consequently, in the presence of postoperative exocrine pancreatic insufficiency, treatment should be tailored to the procedure. After Whipple's procedure, ECPM treatment is the therapy of choice. Following PPPD, however, ECPM treatment will often be ineffective because the microspheres are retained in the stomach. Whether preparations with a smaller sphere size would give a better result remains to be evaluated. The use of conventional powdered pancreatin enzyme preparations, possibly with additional antisecretory treatment, may give greater efficacy in these patients. In patients on ECPM treatment, addition of an H_2-receptor antagonist or proton pump inhibitor may also improve the efficacy of treatment by preventing dissolution of the ECPMs too distally in the gastrointestinal tract.

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References

1 Fish JC, Smith LB, Williams RD. Digestive function after radical pancreaticoduodenectomy. *Am J Surg* 1969; **117**: 40–5.
2 Howard JM. Pancreatico-duodenectomy; forty-one consecutive Whipple resections without an operative mortality. *Ann Surg* 1968; **168**: 629–40.
3 Braasch JW, Gongliang J, Rossi RL. Pancreatoduodenectomy with preservation of the pylorus. *World J Surg* 1984; **8**: 900–5.
4 Schneider MU, Meister R, Domschke S *et al.* Whipple's procedure plus intraoperative pancreatic duct occlusion for severe chronic pancreatitis: clinical, exocrine, and endocrine consequences during a 3-year follow-up. *Pancreas* 1987; **2**: 715–26.
5 Hall RI, Rhodes M, Isabel-Martinez L, Kelleher J, Venables CW. Pancreatic exocrine function after a sutureless pancreatico-jejunostomy following pancreaticoduodenectomy. *Br J Surg* 1990; **77**: 83–5.
6 Trimble IR, Parsons JW, Sherman CP. A one stage operation for the cure of carcinoma of the ampulla of Vater and of the head of the pancreas. *Surg Gynecol Obstet* 1941; **73**: 711–22.
7 Whipple AO. The rationale of radical surgery for cancer of the pancreas and ampullary region. *Ann Surg* 1941; **114**: 612–15.
8 Watson K. Carcinoma of the ampulla of Vater: successful radical resection. *Br J Surg* 1944; **31**: 368–73.
9 Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. *Surg Gynecol Obstet* 1978; **146**: 959–62.
10 Meyer JH, Elashoff J, Porter Fink V, Dressman J, Amidon GL. Human postprandial gastric emptying of 1–3-millimeter spheres. *Gastroenterology* 1988; **94**: 1315–25.
11 Bruno MJ, Hoek FJ, Delzenne B *et al.* Simultaneous assessments of exocrine pancreatic function by the cholesteryl-[^{14}C]octanoate breath test and measurement of plasma *p*-aminobenzoic acid. *Clin Chem* 1995; **41**: 599–604.
12 Borm JJJ, Bruno MJ, de Goeij JJM, Moest TF, van Royen EA. Dosimetric optimization of postproduction neutron-activated erbium-170-oxide-enriched pancreatin. *J Nucl Med* 1995; **36**: 888–92.
13 Borm JJJ, Reinalda WJ, Visser EJ, Wieringa FP, Rienders AJM, van Royen EA. The use of time–location instead of time–activity curves. *Eur J Nucl Med* 1992; **19**: 633(Abstract).
14 Borm JJJ, Tiel-van Buul MMC, van Royen EA. Compressed images and time–location curves for the analysis of two phase gastric emptying studies. First clinical results. *Eur J Nucl Med* 1992; **19**: 644 (Abstract).
15 Cole SG, Rossi S, Stern A, Hofmann AF. Cholesteryl octanoate breath test. Preliminary studies on a new noninvasive test of human pancreatic exocrine function. *Gastroenterology* 1987; **93**: 1372–80.
16 Gyr K, Stalder GA, Schiffmann I, Fehr C, Vonderschmitt D, Farhlaender H. Oral administration of a chymotrypsin-labile peptide – a new test of exocrine pancreatic function in man (PFT). *Gut* 1976; **17**: 27–32.
17 van den Bergh FAJTM, Klein Elhorst JT, Hoek FJ, Tytgat GNJ. Rapid determination of the *p*-aminobenzoic acid excretion index in urine without the use of radioactivity. *Clin Chem* 1986; **32**: 234–5.
18 Roder JD, Stein HJ, Hüttl W, Siewert JR. Pylorus-preserving *versus* standard pancreatico-duodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. *Br J Surg* 1992; **79**: 152–5.
19 Warshaw AL, Torchiana DL. Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. *Surg Gynecol Obstet* 1985; **160**: 1–4.
20 Hunt DR, McLean R. Pylorus-preserving pancreatectomy: functional results. *Br J Surg* 1989; **76**: 173–6.
21 Bruno MJ, Haverkort EB, Tytgat GNJ, van Leeuwen DJ. Maldigestion associated with exocrine pancreatic insufficiency; implications of gastrointestinal physiology and properties of enzyme preparations for a cause-related and patient-tailored treatment. *Am J Gastroenterol* 1995; **90**: 1383–93.