Influence of antacid and formulation on effectiveness of pancreatic enzyme supplementation in cystic fibrosis

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SUMMARY A series of treatment trials, involving food balances based on determination of fat coefficient absorption, nitrogen faecal loss, and daily faecal weight, was performed in 82 patients with cystic fibrosis.

Results showed that a conventional powdered pancreatic extract (Pancrex V) required a high dosage to achieve reasonable improvement in fat and nitrogen absorption (200 mg/kg body weight/day on average) and rarely restored digestion to normal. Bicarbonate (5.2 g/m² body surface/day) slightly enhanced the enzymatic activity of the powdered extract, this being more apparent in those with more severe steatorrhoea. There was no advantage in providing the extract in microgranules protected by cellulose acetatephthalate. A product based on fungal lipase and protease (Krebsilasi) proved to be ineffective in correcting fat and protein absorption. The two recent products prepared in pH sensitive microspheres (Pancrex V microspheres and Pancrease-Prolipase) had similar advantages in digestive activity. Compared with the traditional preparations, they offered a number of practical advantages, including a smaller number of capsules (particularly Pancrex V microspheres) and improved palatability.

Cystic fibrosis is by far the most common cause of pancreatic insufficiency in children.

The use of concentrated pancreatic extracts, obtained mainly from hog pancreas, has played a considerable part for many years in improving the nutritional state of fibrocystic patients.^{1–5} But the limitations of conventional pancreatic extracts have become very apparent, especially in the management of steatorrhoea.^{3–5} Inactivation by the peptic and acid secretion of the stomach plays a fundamental part in this. In the adult it has been shown that only 8% of lipolytic activity and 22% of proteolytic activity administered by mouth can be recovered from the loop of Treitz.⁶ Digestion and absorption of lipids are then further impaired in this disease by deficient secretion of bicarbonate, preventing optimisation of intestinal pH for lipase activity and by deficient lipid micellation due to the reduced pool of bile acids, which are then re-absorbed poorly at the level of the ileum.^{3,7}

Repeated attempts to overcome the gastric effects by formulating the extract in gastroresistant tablets or in granules coated with cellulose acetatephthalate have met with little success.

Few trials have been performed with enzymes of vegetable or bacterial origin, which would have the advantage of not being inactivated in an acid pH.^{8,9} Lingual lipase, whose excellent activity in an acid medium is well known, has not yet been made available for therapeutic use.¹⁰ Use of massive doses of extract has been the main means of overcoming gastric inactivation.⁴ The combined administration of antacids (sodium bicarbonate, aluminium hydroxide, etc) or H₂ receptor antagonists, to reduce gastric acid secretion, has given conflicting results.^{11–13}

A more favourable reception has recently been given to extracts made up in pH sensitive, gastro-protected, and enterosoluble microspheres. These microspheres are stable at pHs below 5.5 and hence the extract is not inactivated in the stomach, while the enzymatic activity is released in 15–30 minutes in an alkaline medium and hence is activated in the small intestine.¹⁴ The small size of the microspheres (diameter less than 3 mm) also allows homogeneous distribution of the extract in the food. Several controlled clinical studies in patients with cystic fibrosis have shown the effectiveness of these

extracts, even if the results are not in complete agreement. Some studies have shown that fat and protein absorption improves compared with conventional extract.¹⁵⁻¹⁷ Others have produced results similar to those obtained with conventional extracts but with a definitely lower daily number of capsules and without the unpleasant taste of the powdered pancreatic extract, thus leading to better therapeutic compliance.^{2 13 14 18}

Interpretation of these clinical trials is generally difficult because of the small number of patients studied, especially as it is a therapeutic field in which individual variability plays an important part in influencing the results. This study describes research into the possible beneficial effect of antacids, looks at any advantages of pancreatic extracts in pH sensitive microspheres, and compares the old and new extracts available on the market today, using a larger number of patients with cystic fibrosis.

Patients and methods

In all patients included in this study the diagnosis of cystic fibrosis was made on the basis of at least two sweat tests, using the Gibson and Cooke procedure.

In most of the patients a study was then made of pancreatic function by duodenal intubation, stimulation with a secretin-pancreozymin bolus (2 U/kg body weight), and determination of the enzyme and bicarbonate output for 30 minutes.¹⁹ In addition, a food balance was carried out for three to four days, with determination of the coefficient of fat absorption (ACfat), faecal nitrogen loss, and daily faecal

weight. The food balance during treatment with pancreatic extracts or antacids was made under hospital conditions: the start and end of each balance was marked by oral administration of carmine. During each balance a diet was given with strictly controlled fat content (from 2 to 4 g/kg/day according to age; average 3 g/kg/day), while the protein and carbohydrate content were balanced but uncontrolled. When pancreatic extracts were administered the number of capsules given each day was calculated and rounded individually around the chosen dosage, distributed over the four daily meals and divided during the meal into start, middle, and end. When two extracts were compared in the same subjects priority was randomly assigned.

The following variables were recorded for the faeces in each period: faecal fats by Van de Kamer's method, as modified by Jeejeebhoy for medium chain triglyceride fats,²⁰ with calculation of the coefficient of absorption, and daily faecal nitrogen determined on a Carlo Erba ANA automatic analyser.²¹ The means of the results obtained for paired groups were compared by Student's *t* test.

Consent was obtained from the parents or patients, or both, after adequate explanation.

The declared characteristics and composition of the different pancreatic extracts used are set out in Table 1.

The gastroprotective coating of the two pH sensitive compounds is made from cellulose acetatephthalate, plasticised with diethylphthalate. Of the other excipients, which are the main constituents of microsphere cores, the composition was available

Table 1 Declared characteristics and composition of the different pancreatic extracts used

Pancreatic extract (Manufacturers)	Form of preparation*	Weight of contents of one capsule (mg)	Declared active substance	Declared content of FIP [‡] units in one capsule		
				Lipase	Amylase	Protease
Pancrex V powder (Samil-Pabyrn)	Powder (in capsules)	340	Pig pancreatin BP 340 mg	13000	10500	550
Pancrex V granular (Samil-Pabyrn) [†]	Gastroresistant microgranules (cellulose acetate-phthalate) in capsules	500	Pig pancreatin BP 420 mg	15000	13000	680
Pancrex V microsphere (Samil-Pabyrn)	Gastroresistant, enterosoluble, pH sensitive microspheres in capsules	500	Pig pancreatin BP 340 mg	13000	10500	550
Pancrease-Prolipase (Cilag)	Acid resistant, enterosoluble, pH sensitive microspheres (in capsules)	420	Pig pancrelipase	5000	2900	330
Krebsilasi (Irbi)	Separate tablets (in capsules)	500	Ox pancreatin and fungal enzymes	7500	9000	350

*All the enzymatic preparations are contained in hard gelatin capsules.

[†]The granular preparation in the Italian market has different characteristics from a similar preparation in Britain.

[‡]FIP=Federation Internationale Pharmaceutique.

for the Pancrex V microspheres* only—namely, amidocarboxyethylate, polyvinyl pyrrolidone, saccharose, starch, talc, and E171.

The dosage of pancreatic extracts was standardised on the basis of our previous study,⁴ in which a relation between dose and effect was found for Pancrex V powder: 200 mg/kg/day, corresponding to about 75 mg of extract per gram of fat administered, resulted in the most acceptable and reasonable dose. Adequate adjustments were made for the new preparations Pancrease-Prolipase and Pancrex V microspheres.

The overall study was made in successive stages as briefly described below.

Phase I: effect of sodium bicarbonate. The effect of sodium bicarbonate in combination with Pancrex V powder was tested in 40 patients with cystic fibrosis. Of these, 26 (mean (SD) age 5.09 (4.12) years) were treated with this conventional extract and then with the same extract plus sodium bicarbonate (5.2 g/m² body surface/day). The other 14 (mean (SD) age 5.56 (4.05) years) constituted the control group, in whom the only treatment, alternating with two basal balance phases, was sodium bicarbonate.

Phase II: comparison between conventional powdered pancreatic extracts and gastroresistant granules. Pancrex V powder and Pancrex V microgranules† were compared in six patients with cystic fibrosis (mean (SD) age 10.2 (5.3) years) according to the same dosage as in phase I.

Phase III: comparison between conventional powdered pancreatic extracts and extracts in pH sensitive, gastroprotected, and enterosoluble microspheres. Three comparative trials were made in succession (Table 2).

(A) Pancrex V powder versus a pH sensitive extract (Pancrease-Prolipase) in 11 patients with

cystic fibrosis (mean (SD) age 9.5 (4.2) years) with the same quantity of extract by weight.

(B) Pancrex V powder versus a second pH sensitive extract (Pancrex V microspheres) in 10 patients with cystic fibrosis (mean (SD) age 8.3 (4.7) years). For Pancrex V microspheres it was decided to administer a dose that would provide lipase activity equal to that of the administration of Pancrease-Prolipase in the preceding group.

(C) The first (Pancrease-Prolipase) versus the second (Pancrex V microspheres) pH sensitive extract in 10 patients with cystic fibrosis (mean (SD) age 10.6 (6.1) years). The dosage used for Prolipase-Pancrease was 70–100 mg/g fat and for Pancrex V microspheres was a quantity by weight that would supply the same activity as the preceding extract (35–50 mg/g fat).

It should be pointed out that, in view of the presumed advantages of the pH sensitive compounds, the quantity of lipase activity administered with these corresponded to about a third of the lipase activity of Pancrex V powder.

For the preparations administered to infants unable to swallow capsules, the microspheres were mixed with grated apple, which has an acid pH: this procedure did not create any problems.

Phase IV: pancreatin with enzymes of fungal origin. The digestive effect of the product Krebsilasi (pancreatin with enzymes of fungal origin) was studied, with the criteria previously described, in five patients with cystic fibrosis (mean (SD) age 8.1 (1.8) years) in comparison with their baseline digestive situation. With regard to dosage, the mean (SD) quantity of capsules (12 (1.7) per day) administered each day was such as to supply a lipase activity roughly equal to that of the pH sensitive formulations (1496.4 (277.8) FIP (Federation Internationale Pharmaceutique) lipase units per gram of fats administered).

Results

Effect of bicarbonate. Figure 1 shows individual and

*Pancrex V microspheres are not commercially available at the time of writing.

†Pancrex V microgranules in capsules are an experimental formulation not commercially available.

Table 2 Treatment schedule with different pancreatic extracts in five groups of patients. Values are mean (SD) [range] except where stated

Group	No of patients	Baseline ACfat (%)	First pancreatic extract	Mean (SD) No of capsules/day	ACfat (%)	Faecal nitrogen (g/day)	Faecal weight (g/day)	Second pancreatic extract	Mean (SD) No of capsules/day	ACfat (%)	Faecal nitrogen (g/day)	Faecal weight (g/day)
1	6	36.2 (16.6) [21.6–65.8]	Pancrex V powder	16.3 (3.3)	65.7 (16.8) [35.7–82.8]	2.73 (1.17) [1.41–4.74]	265 (159) [137–601]	Pancrex V microgranules	16.3 (3.3)	68.1 (22.1) [30.7–87.2]	2.23 (1.30) [1.21–5.09]	216 (131) [124–507]
2	11	41.1 (14.7) [19.0–73.0]	Pancrex V powder	16.3 (2.0)	70.7 (21.6) [22.3–93.7]	2.03 (1.14) [0.85–4.50]	207 (90) [79–442]	Pancrease-Prolipase	14.0 (1.7)	86.2 (13.5) [47.3–97.2]	1.40 (0.26) [1.10–2.09]	168 (37) [107–259]
3	10	48.8 (15.8) [25.0–65.6]	Pancrex V powder	16.8 (3.8)	78.2 (16.2) [52.1–96.7]	1.46 (0.37) [0.87–2.20]	137 (57) [77–228]	Pancrex V microspheres	7.0 (1.0)	83.9 (11.8) [55.2–96.0]	1.59 (0.44) [1.01–2.37]	177 (52) [115–292]
4	10	44.3 (18.9) [27.0–66.2]	Pancrease-Prolipase	14.6 (3.4)	87.3 (6.3) [73.3–93.9]	1.98 (0.98) [0.78–3.81]	181 (97) [72–420]	Pancrex V microspheres	6.6 (1.2)	86.5 (7.6) [66.9–95.4]	2.09 (1.46) [0.90–5.85]	162 (96) [73–384]

Fig. 1 Fat absorption coefficient, obtained by three subsequent food balances in different treatment conditions in two groups of patients with cystic fibrosis. The 'treated' group received pancreatic extract (Pancrex V powder, about 200 mg/kg body weight/day) or pancreatic extract (Pancrex V, same dose) plus sodium bicarbonate (about 5.2 g/m² body surface/day); the 'control' group was treated with sodium bicarbonate alone (5.2 g/m² body surface/day).

mean changes obtained in ACfat in patients with cystic fibrosis through the effect of pancreatic extract (Pancrex V powder) and through the effect of combining sodium bicarbonate with the extract, in comparison with a group of patients with cystic fibrosis treated with sodium bicarbonate alone. It is clear that by itself bicarbonate did not produce any effect, while its effect in combination with the extract was measurable but of little importance. There was a wide variation in response, presumably linked to the baseline absorption condition. Bicarbonate seemed in fact to have an enhancing effect on lipase activity, which was higher for patients with lower baseline ACfat; in patients with a baseline ACfat over 75% bicarbonate proved to be completely ineffective. Figure 2 shows individual and mean changes obtained for daily nitrogen loss in the same groups of subjects under the same treatment conditions. There was the usual wide variability of results, evident even in the control group.

Combining bicarbonate with the extract did not seem to affect the degree of azotorrhoea found with the extract alone. No change was observed in acid base equilibrium of the blood with the bicarbonate dosage used.

Comparison between two commercial forms of concentrated pancreatic extract (powder and microgranules). The results showed no differences between the mean values of ACfat, azotorrhoea, and daily faecal weight (Table 2). In view of these results, a fuller comparison was not made.

Evaluation of pancreatic extracts in gastroresistant and enterosoluble microspheres. (Fig. 3) The mean value of ACfat was about 86% with Pancrease-Prolipase compared with 71% with the conventional Pancrex V powder ($p<0.05$); there was no significant difference, on the other hand, as regards faecal

nitrogen and daily faecal weight (Table 2). The ACfat obtained with Pancrex V microspheres was on average higher than that obtained with Pancrex V powder, even though the difference was not significant. There were no significant differences as regards azotorrhoea and daily faecal weight (Table 2).

In 10 patients the direct comparison between Pancrease-Prolipase and Pancrex V microspheres showed similar results for ACfat (average 87% and 86%, respectively), faecal nitrogen (mean 1.98 g/day and 2.09 g/day, respectively), and daily faecal weight (180 g/day and 160 g/day, respectively).

When the individual cases were examined the results were still similar.

Cumulative results. The overall data of the comparative clinical trials covered by the last two subheadings are summarised in Table 3, combining the cases from all treatment groups.

It can be seen that the pH sensitive formulations were more effective than the conventional ones as regards fat absorption, while there was no significant difference for loss of faecal nitrogen or daily faecal weight. Likewise, the comparison between the conventional powdered extract and its form in gastroprotected microspheres (Pancrex V), which showed no significant differences in the small trial, showed definite advantages for the microsphere form when all patients were considered together.

This effect was obtained with a lower activity of lipase per gram of fat and a decidedly smaller number of capsules each day. With the new gastro-protected and enterosoluble compounds mean ACfat values of about 85% were obtained: out of a total of 31 patients and a total number of 41 food balances, during which one or other of these extracts was administered, the improvement in digestion was excellent (ACfat over 90%) in 18, good (ACfat

Table 3 Cumulative comparison between four types of pancreatic extract, with determination of fat absorption coefficient (ACfat), daily faecal nitrogen, and daily faecal weight (74 food balance tests in 37 patients with cystic fibrosis)

Pancreatic extract	No of food balance tests	Mean (SD) age (years)	Mean (SD) No of capsules/kg/day	Mean (SD) FIP lipase units per gram of fat administered	Mean (SD) FIP Protease units per gram of fat administered	Mean (SD) [range] baseline ACfat (%)	On treatment (mean (SD) [range])		
							ACfat (%)	Faecal nitrogen (g/day)	Faecal weight (g/day)
Pancrex V powder	27	9.2 (4.7)	0.74 (0.20)	3313.1 (506.9)	140.1 (21.4)	47.8 (16.5) [18.3-79.1]	72.3 (19.3) [22.3-97.1]	1.97 (1.05) [0.85-4.74]	194.1 (111.9) [77-601]
Pancrex V microgranules	6	10.2 (5.3)	0.70 (0.15)	3182.0 (477.8)	166.4 (24.9)	36.2 (16.6) [18.3-65.8]	68.1 (22.1) [30.7-94.4]	2.23 (1.30) [1.21-5.09]	216.4 (131.0) [124-507]
Pancrease-Prolipase	21	10.0 (5.2)	0.54 (0.18)	1034.8 (180.2)	68.2 (11.8)	42.8 (17.2) [4.0-73.0]	86.7 (10.7) [47.3-97.2]	1.68 (0.76) [0.78-3.81]	174.1 (72.4) [72-420]
Pancrex V microspheres	20	9.4 (5.5)	0.25 (0.14)	1327.7 (457.6)	56.1 (19.3)	46.4 (17.7) [4.0-79.1]	85.2 (10.0) [55.2-96.0]	1.84 (1.10) [0.90-5.85]	169.5 (77.7) [73-384]

Comparison of means between treatments (S=significant ($p<0.05$); SS=highly significant ($p<0.01$); NS=not significant ($p>0.05$)).

ACfat:	Faecal nitrogen:	Faecal weight:	ACfat:	Faecal nitrogen:	Faecal weight:
1 v 2 $p>0.6$ (NS)	$p>0.6$ (NS)	$p>0.8$ (NS)	2 v 3 $p<0.05$ (S)	$p>0.3$ (NS)	$p>0.4$ (NS)
1 v 3 $p<0.01$ (SS)	$p>0.2$ (NS)	$p>0.4$ (NS)	2 v 4 $p<0.05$ (S)	$p>0.5$ (NS)	$p>0.4$ (NS)
1 v 4 $p<0.01$ (SS)	$p>0.6$ (NS)	$p>0.3$ (NS)	3 v 4 $p>0.6$ (NS)	$p>0.5$ (NS)	$p>0.8$ (NS)

Fig. 2 Daily faecal nitrogen determined by three subsequent food balances in different treatment conditions in two groups of patients with cystic fibrosis. The 'treated' group received pancreatic extract (Pancrex V powder, about 200 mg/kg body weight/day) or pancreatic extract (Pancrex V, same dose) plus sodium bicarbonate (5.2 g/m² body surface/day); the 'control' group was treated with sodium bicarbonate alone (5.2 g/m² body surface/day).

75–90%) in 18, and insufficient (ACfat lower than 75%) in only five.

With the conventional extract, out of a total of 27 treated patients and a total number of 27 food balances, there were only six in whom the ACfat was over 90%, while in seven it was between 75 and 90%, and in 14 it was well below 75%.

Evaluation of a product containing fungal lipase and protease (Krebsilasi). Baseline ACfat was not modified at all by this product (from a mean (SD) of 47 (15.5) % to 49.5 (13.6) %); faecal nitrogen improved to a very limited extent (from a mean (SD) of 4.82 (1.5) g/day to 3.82 (2.2) g/day) compared with the results obtained from the other products. A similar trend was observed for daily faecal weight (from 357.7 (102.8) g/day to 246.4 (55.4) g/day). There was no significant difference in the variables measured between the baseline situation and after treatment.

Discussion

By using bicarbonate with a conventional extract it is possible to obtain an improvement in the digestive effect of the extract on fats, though this is limited. The effect is greater when the baseline steatorrhoea is more severe, and it is quantitatively comparable with that obtainable with cimetidine.^{11–13} No improvement in azotorrhoea can be obtained with bicarbonate. On the other hand, the overall faecal loss of nitrogen with the conventional extracts at high doses approaches closely to normal loss.

The preparations formulated to protect the extract against gastric inactivation were therefore considered with interest. Simple protection with cellulose acetatephthalate, as in the Pancrex V microgranules preparation, did not show any advantage. On the other hand, the preparations in pH sensitive gastroresistant and enterosoluble microspheres manufactured using more up to date methods were shown in our work to offer advantages. This conclusion was based on a larger set of cases than has generally been reported previously.^{2 13 14 16–18} Such preparations were undoubtedly more active in promoting fat absorption than the unprotected extracts. No improvement was evident, however, in loss of faecal nitrogen or daily faecal weight.

These results should be compared with those obtained by other workers, who have not always shown greater efficacy of the new types of formulation but only shown greater practicability.^{2 13 18} In other words, they have usually stated that the same effect can be obtained with a smaller dose of pH sensitive extract compared with the conventional extracts.

Fig. 3 Two groups of patients with cystic fibrosis were treated alternatively with a conventional pancreatic extract and new pH sensitive formulations ((a) and (b), respectively); a third group was treated with two different new formulations (c). Fat absorption coefficients on different treatments are compared with the baseline ones.

Much of the reported work on pancreatic extracts has been based on excessively small samples.^{2 13-18} In none of the experiments was the dosage related to the quantity of fats introduced, while evaluation of the results was often performed using ill defined variables.¹⁷ It is acknowledged that this type of trial is somewhat difficult from the methodological standpoint. There is in fact great variability of results from case to case, and it is difficult to obtain well matched groups of patients. It is enough to observe that in our experiments three groups of subjects (numbering six, 11, and 10, respectively), treated with the same dosage of Pancrex V powder, gave three widely differing mean values for ACfat—namely, 65, 70, and 78%, respectively. Only comparing patients in large groups, as was made possible by the complex design of this experiment, allowed a reliable and statistically valid comparison to be made between the different pancreatic extracts.

We are unable to say whether the results obtained with recent extracts can be produced with even

lower dosages than those used, but it must be reiterated that they were obtained with an intake of enzymatic activity of about a third of that which had given the best but not optimal activity with the powdered pancreatic extracts, on the basis of a progressive dosage test.⁴

The product based mainly on acid stable enzymes of fungal origin proved to be ineffective in correcting steatorrhoea and azotorrhoea in patients with cystic fibrosis.

Lastly, it should be pointed out that there are resistant cases (perhaps 10%) in whom no type of pancreatic extract nor any dietary addition can bring the digestion to acceptable equilibrium. These are the cases with either extensive ileal resection for meconium ileus or possible severe deficiency of resorption of bile acids.^{7 13} In these cases we have found that inhibition of gastric acid secretion by means of H_2 antagonists has occasionally been successful, while there is the possibility of gaining some advantage by the use of bile salts to improve micellar concentration.

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