A double blind lipase for lipase comparison of a high lipase and standard pancreatic enzyme preparation in cystic fibrosis

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Abstract

A standard acid resistant microsphere pancreatic enzyme preparation was compared with identical capsules half filled with minitabets of a new high lipase preparation in a randomised double blind crossover study in children with cystic fibrosis. Each patient received his/her usual number of capsules and the same dose of lipase during each period of the study. Eighteen patients completed the study. There were fewer gastrointestinal symptoms when pancreatic enzyme was supplied as the high lipase preparation. There was also a significant improvement in fat absorption (17%, 95% confidence interval (CI) 6 to 27), reduction in faecal fat output (15.8 g/day, 95% CI 6.4 to 22.5), and faecal energy loss (789 kJ/day, 95% CI 211 to 1384). It is concluded that half filled capsules of the new high lipase preparation are more effective than the standard preparation and it is likely that filled capsules would allow patients to use fewer than half the number of pancreatic enzyme capsules.

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Pancreatic insufficiency affects 85-90% of patients with cystic fibrosis and is the main cause of their intestinal malabsorption.¹ This results in high energy losses in the stools,² which, together with reduced intake and an increased energy expenditure,^{3,4} may compromise the patient's nutritional state and prognosis.^{5,6}

Many patients experienced an impressive improvement in their symptoms in intestinal malabsorption when they changed from the traditional pancreatic extracts to acid resistant microspheres. Also, many were then able to tolerate a normal or even generous fat intake, thus improving their total energy intake.⁷ The improved absorption of fat and nitrogen after the change to the acid resistant microspheres is well documented.⁸⁻¹⁰

There are, however, many patients who require large doses of an acid resistant microsphere preparation (either Creon, Duphar; Pancrease, Cilag; or Nutrizym GR, Merck) to achieve reasonable control of fat malabsorption as judged by their symptoms, or, more commonly, by an acceptable coefficient of fat absorption (absorption of more than 85% of ingested fat). In a few patients adequate fat absorption is not achieved.

The purpose is this trial was to determine whether control of malabsorption could be maintained when the same dose of pancreatic

enzyme was supplied in a high lipase preparation as in a standard acid resistant microsphere preparation. If the requirement for pancreatic enzyme capsules in patients with cystic fibrosis currently needing moderate or large numbers could be substantially reduced, this would represent a significant improvement in the quality of the patients' everyday lives, and may help to improve compliance.

Patients and methods

Twenty one patients from the Leeds cystic fibrosis clinic were enrolled in the study (median age 11.5 years, range 4.9-14.1 years). All had classical features of cystic fibrosis and had had two measurements of sweat sodium and chloride concentrations greater than 60 mmol/l.¹¹

The patients had a median weight for age of 99% (94-116) and weight for height of 94% (82-126) and had a median forced vital capacity 94% of predicted (45-136).¹² Their median Chrispin-Norman chest x ray score was 10 (2-32)¹³ and Shwachman score 85 (50-95).¹⁴ Their previous median faecal fat output was 7.0 g/day (1.6-31.5).

Patients were included in the study if they required greater than 15 pancreatic enzyme capsules daily (median 30; range 15-100). Before the study, all were taking microsphere preparations: Creon or Pancrease. Patients were excluded if they were unable to ingest pancreatic enzymes without opening the capsules or if they were considered unlikely to be able to complete the trial protocol.

STUDY DESIGN

Each patient completed a three day dietary diary before the commencement of the study from which the patient's average intake of dietary fat was determined. Using these data a paediatric dietitian instructed the patients and parents on how to maintain a relatively constant fat diet (within 5 g/day of the usual intake) during the two treatment periods.

The trial had a double blind randomised crossover design. It was estimated that 24 patients would be required to detect a 10% change in faecal fat with a 90% power at the 95% level of significance.

The patients were randomly assigned to receive either a standard acid resistant microsphere pancreatic enzyme preparation (Nutrizym GR) or an identical capsule half filled with minitabets of an acid resistant high lipase preparation (Nutrizym 22, Merck) in the first treatment period (table 1). The lipase content of

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Table 1 Enzyme content of capsules*

	Declared content of fully filled capsules		Actual content of capsules used in the study†	
	Nutrizym GR	Nutrizym 22	Nutrizym GR	Nutrizym 22
Lipase (BP units)	10000	22000	11100	11800
Amylase (BP units)	10000	19800	12000	13300
Protease (BP units)	650	1100	740	815

*Manufacturer's data.

†Half filled capsules of Nutrizym 22 were used in the study.

each capsule was therefore almost identical. The patients were instructed to take the same numbers of each trial capsule as they would have normally administered of their usual enzyme preparation for a two week period. This was followed consecutively by a further two week period of the alternative treatment without a 'washout' (fig 1). Thus each patient received the same lipase dose in the same number of capsules throughout the study.

Two day faecal collections were undertaken at the end of each treatment period while the patient was taking radio-opaque markers.¹⁵ Faecal fat was determined using the method of van de Kamer *et al*,¹⁶ and faecal nitrogen content assayed using a Tecator Kjeltac Auto Model 1030 nitrogen analyser. Faecal energy content was derived from wet stool weight using the regression equations of Murphy *et al*.²

A daily dietary diary was completed during the last five days of each treatment period and the intake of fat, total nitrogen, and energy was assessed by a paediatric dietitian using the McCance and Widdowson nutrient data¹⁷ on the Microdiet computer software.¹⁸

Throughout the study each patient completed a simple subjective symptom diary. Normal stool character was recorded as 0, pale or loose stools as 1, and very pale or loose stools as 2. The number of stools passed each day was also recorded. Abdominal pain and abdominal distension were recorded on a 0–2 scale, but these symptoms were analysed as present or absent. For purposes of analysis the final seven days of each treatment period was used.

Informed consent was obtained from the patients and parents. The study protocol was

approved by the hospital research ethics committee.

STATISTICAL ANALYSIS

Statistical analysis was undertaken using the Minitab computer statistics package.¹⁹ Tests for differential carry over and period effects were assessed at the 90% significance level due to the low power of the tests. As the tests were negative in each case the Wilcoxon signed rank test for paired data was used for analysis of the faecal output and absorption data. The symptom scores were averaged for each patient. Given evidence of the differential carry over, an unpaired analysis of the difference between the average symptom scores of the two groups was carried out for the first period only, using a Mann-Whitney test.

Results

Eighteen patients completed the study. Three patients withdrew because of increased symptoms of intestinal malabsorption while receiving Nutrizym GR and no faecal collection was made by them while receiving that treatment. Faecal nitrogen data was not available on a further three patients because of difficulties encountered with pH changes in the stool collections during storage before analysis.

There were no significant difference in age, enzyme intake, nutritional state, or respiratory function between the patients who received treatment in the order Nutrizym 22, Nutrizym GR, or vice versa. There was also no significant differential carry over for faecal fat output ($p=0.37$), fat absorption ($p=0.38$), faecal output of energy ($p=0.43$), or faecal nitrogen ($p=0.48$).

FAT ABSORPTION, ENERGY, AND NITROGEN OUTPUT

These results are summarised in table 2. When pancreatic enzyme was supplied as Nutrizym 22 fat absorption was increased by 17%/day (fig 2), faecal fat output was reduced by 15.8 g/day, and

Figure 1 Scheme of trial. The patients were maintained on a relatively constant fat diet during the two treatment periods; C=faecal collection.

Table 2 Faecal output and absorption results

	Nutrizym 22 Median (range)	Nutrizym GR Median (range)	Treatment difference	95% CI for treatment difference	Statistical significance of difference
Fat absorption (%)	91 (57–97)	76 (9–92)	17	(6 to 27)	0.002
Faecal fat output (g/day)	8.7 (2.2–52.8)	26.1 (7.5–57.7)	–15.8	(–22.5 to –6.4)	0.003
Faecal energy output (kJ/day)	1195 (640–3702)	2040 (943–4796)	–789	(–1384 to –211)	0.027
Faecal nitrogen output (g/day)	2.4 (0.7–7.1)	2.7 (1.3–9.6)	–0.88	(–1.65 to 0.2)	0.08

Table 3 Median symptom scores during last seven days of period 1

	No	Mean	Median	95% CI of difference in median* (p value)
(A) Stool character:				
Nutrizym 22	11	0.335	0.143	-1.143 to 0.143 (0.19)
Nutrizym GR	10	0.783	0.905	
(B) Stool number:				
Nutrizym 22	11	2.028	1.714	-1.286 to 0.166 (0.10)
Nutrizym GR	10	2.419	2.286	
(C) Abdominal pain:				
Nutrizym 22	11	0.27	0.29	-0.43 to 0.29 (0.46)
Nutrizym GR	10	0.34	0.29	

*By Mann-Whitney.

Figure 2 Fat absorption.

energy losses in the stools were reduced by 789 kJ/day. The faecal output of nitrogen was reduced by 0.88 g/day but this did not reach statistical significance at the 95% level due to smaller numbers than expected.

We compared the faecal fat output while receiving each treatment with the patients' most recent measurement before the trial. When receiving Nutrizym 22 there was no significant difference (difference 0.65 g/day; 95% confidence interval (CI) -3.05 to 4.6; $p=0.45$), however the faecal fat was significantly greater than the previous record when the patients were receiving Nutrizym GR (difference 15.3 g/day; 95% CI 11.8 to 23.8; $p<0.0001$).

SYMPTOM SCORES

The patients receiving Nutrizym GR reported more severe symptoms compared with Nutrizym 22 (table 3A-C). The median score for the character of stools was 0.9 in the Nutrizym GR group compared with 0.14 in the Nutrizym 22 group (table 3A), and for the number of stools 2.3 compared with 1.7 (table 3B). Neither of these differences were statistically significant. The two groups had similar levels of pain (table 3C) and swelling. The latter symptom was reported on only three patient days during treatment with Nutrizym GR.

Discussion

We have demonstrated that the provision of pancreatic enzyme in the form of the new high

lipase minitablets was more effective than as standard acid resistant microspheres. We had expected to demonstrate equal efficacy of Nutrizym GR and half filled capsules of Nutrizym 22. However, the superiority of the latter preparation both in terms of improved absorption of fat, reduced faecal nitrogen and energy loss, and reduced symptoms of intestinal malabsorption suggests that when administered as fully filled capsules, Nutrizym 22 may allow patients with cystic fibrosis to use fewer than half the number of pancreatic enzyme capsules.

Only one previous study has reported the clinical use of a high lipase pancreatic enzyme preparation.²⁰ However, this was an open study, the two enzyme preparations were compared in a fixed order and the dosage of lipase was not standardised. It has been suggested that some patients receiving high doses of pancreatic enzyme may be able to reduce their daily dose of enzyme capsules without appreciable deterioration of their fat absorption or symptoms,²¹ and therefore we used a randomised double blind crossover design and employed half filled capsules to avoid the bias of reduced capsule numbers. An alternative study design using containers of both active medication and placebo during the high lipase arm of the study was considered, but this would have introduced additional complexity and required patients to carry two containers of medication at all times.

The three patients who withdrew from the study were receiving Nutrizym GR. This enzyme has not been the subject of previous clinical trials but its predecessor, Pancreatin Merck, was found to be somewhat less effective than both Creon and Pancrease.⁸ The patients' faecal fat output when receiving Nutrizym GR during this study was also significantly greater than their most recent determination of faecal fat before commencement of the study.

Nutrizym GR contains microspheres of between 1.13 and 1.88 mm which have been considered to be of an ideal size for ensuring that the spheres empty from the stomach at the same rate as food.²² Nutrizym 22 contains minitablets that are coated in an acid resistant membrane, allowing a high degree of gastric protection at pH 5, but with prompt release of enzyme above pH 5.5 (J Kelleher, unpublished, data on file E Merck Pharmaceuticals). Although the minitablets are considerably larger (2.2 mm), it would appear that the greater particle enzyme concentration can more than compensate for the larger size in determining clinical efficacy.

Acid resistant microspheres were a major development in the management of intestinal malabsorption in cystic fibrosis allowing patients to consume a normal fat diet and maintain the best nutritional status. We have now shown that pancreatic enzyme delivered in a high lipase preparation can not only maintain the intestinal absorption of cystic fibrosis patients, but indeed can improve that absorption over that achieved by a standard preparation. This should allow a considerable reduction in the number of pancreatic enzyme capsules that a pancreatic insufficient patient needs to take and is likely to result in an improvement in patient compliance.

We conclude that high lipase minitabets of Nutrizym 22 are effective in the control of intestinal malabsorption in cystic fibrosis and their use will allow a considerable reduction in the number of enzyme capsules required.

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