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 minitablets 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 eat 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.3,6

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 of 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 Schwachman 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 minitablets of an acid resistant high lipase preparation (Nutrizym 22, Merck) in the first treatment period (table 1). The lipase content of
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 with-
out 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 Tectar Kjeltec Auto
Model 1030 nitrogen analyser. Faecal energy
content was derived from wet stool weight using
the regression equations of Murphy et al.17

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 dietician using the
McCance and Widdowson nutrient data18 on the
Microdiet computer software.19

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 symp-
toms 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 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). See 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% g/day, and

### Table 2 Faecal output and absorption results

<table>
<thead>
<tr>
<th></th>
<th>Nutrizym 22</th>
<th>Nutrizym GR</th>
<th>Treatment difference</th>
<th>95% CI for treatment difference</th>
<th>Statistical significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat absorption (%)</td>
<td>91 (57–97)</td>
<td>76 (9.92)</td>
<td>17</td>
<td>(6 to 27)</td>
<td>0.002</td>
</tr>
<tr>
<td>Faecal fat output (g/day)</td>
<td>8.7 (2.2–5.8)</td>
<td>26.1 (7.5–57.7)</td>
<td>-15.8</td>
<td>(-22.5 to -6.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Faecal energy output (kJ/day)</td>
<td>1195 (646–3702)</td>
<td>2040 (943–4706)</td>
<td>-789</td>
<td>(-1384 to -211)</td>
<td>0.027</td>
</tr>
<tr>
<td>Faecal nitrogen output (g/day)</td>
<td>2.4 (0.7–7.1)</td>
<td>2.7 (1.3–9.6)</td>
<td>-0.88</td>
<td>(-1.65 to 0.2)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 1  Enzyme content of capsules

<table>
<thead>
<tr>
<th></th>
<th>Nutrizym GR</th>
<th>Nutrizym 22</th>
<th>Nutrizym GR</th>
<th>Nutrizym 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase (BU units)</td>
<td>10000</td>
<td>22000</td>
<td>11100</td>
<td>11800</td>
</tr>
<tr>
<td>Amylase (BU units)</td>
<td>650</td>
<td>1100</td>
<td>740</td>
<td>815</td>
</tr>
<tr>
<td>Protease (BU units)</td>
<td>10000</td>
<td>19800</td>
<td>12000</td>
<td>13300</td>
</tr>
</tbody>
</table>

*Manufacturer’s data.
†Half filled capsules of Nutrizym 22 were used in the study.

Figure 1  Scheme of trial. The patients were maintained on a relatively constant fat diet during the two treatment periods; C=faecal collection.
Table 3 Median symptom scores during last seven days of period 1

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

*By Mann-Whitney.

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 capsules. 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.22 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 minitablets 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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