Comparison of four pancreatic extracts in cystic fibrosis

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SUMMARY Four different pancreatin products, Pancrease, Creon, Pancrex V Forte, and Pancreatin Merck, were compared in a random crossover trial in children with cystic fibrosis. The results of our study showed that patients who received Creon and Pancrease had fewer gastrointestinal symptoms than patients who received Pancrex V Forte and Pancreatin Merck. Fat absorption was significantly improved with Pancrease when compared with Pancrex V forte and Pancreatin Merck. Also the fat absorption with Creon was superior to that with Pancrex V Forte. There was no significant difference in fat absorption between Pancrease and Creon, Pancrex V Forte and Pancreatin Merck, or Pancreatin Merck and Creon. Faecal nitrogen content was less with both Creon and Pancrease compared with Pancreatin Merck.

Creon and Pancrease allow the patient with cystic fibrosis to take a high energy diet without any dietary restrictions.

Pancreatic insufficiency occurs in most patients with cystic fibrosis. Supplementation with adequate doses of pancreatic extracts decreases the number and bulk of stools and improves growth. There is, however, a great deal of variability between the different preparations and patients’ responses to them. The older preparations have been shown to provide less than 8% of ingested lipase activity at the ligament of Trietz as a consequence of acid/pepsin digestion in the stomach. Recent studies have shown that a microsphere system of delivering enzyme preparations significantly enhances fat absorption compared with conventional enzyme preparations. The microspheres are administered in a gelatin capsule that dissolves in the stomach. The pancreatic in the released microspheres is protected from acid/pepsin digestion by a pH sensitive coat that does not dissolve until the pH exceeds roughly 5-5. Thus the granules mix with the gastric contents and enzymes are not released until the pH of the chyme exceeds 5-5 within the duodenum. In this study we compared the efficacy of Pancrex V Forte tablets (Paines and Byrne) with three microsphere systems—namely, Pancrease (Ortho-Cilag), Creon (Duphar), and a new pancreatic product, Pancreatin Merck (Merck Pharmaceuticals) (Table).

Patients and methods

Patients. Nineteen patients who were currently receiving treatment at our unit were enrolled in the study. Their median age was 12 years 1 month, with a range of 6 years 2 months to 20 years 1 month, and their most recent Shwachman clinical scores and Chrissin Norman x ray scores were 80 (60–95) and 6 (0–21), respectively. All children had symptoms of cystic fibrosis and all had had at least two raised sweat sodium and chloride concentrations. At the time of entry into the trial all patients were on an unrestricted normal diet that contained a median of 3·14 (1·38–4·48) g of fat/kg/day and were receiving as their pancreatic supplement a median of 18 (6–40) capsules of Pancrease each day.

Table Enzyme content of the four different preparations used in the study

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Manufacturers</th>
<th>Lipase</th>
<th>Amylase</th>
<th>Protease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrex V Forte</td>
<td>Paines and Byrne</td>
<td>5600</td>
<td>5000</td>
<td>330</td>
</tr>
<tr>
<td>Creon</td>
<td>Duphar</td>
<td>8000</td>
<td>9000</td>
<td>210</td>
</tr>
<tr>
<td>Pancrease</td>
<td>Ortho-Cilag</td>
<td>5000</td>
<td>2900</td>
<td>330</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>Merck</td>
<td>7700</td>
<td>10 000</td>
<td>650</td>
</tr>
</tbody>
</table>
Study design. (Fig. 1). The study in each patient was undertaken over seven weeks. During the initial run in, a seven day dietary assessment was undertaken to determine the average daily fat intake. The patients and parents were instructed about the principles of a constant fat diet and during weeks 1, 3, 5, and 7 the parents weighed and recorded each portion of food to ensure a constant daily fat intake, the amount of fat taken being similar to the normal fat intake of their child. Although we did not use a constant protein diet, we assessed the protein intakes of five patients during the four study weeks of the trial. These were all well controlled and for this reason dietary protein assessment was not undertaken in the other patients. The dietary management was closely supervised by a paediatric dietitian (AM).

Pancreatic extract was given during the study as follows. In week 1 the patients continued to take their usual amount of Pancrease each day, ensuring the same daily total number of capsules. The patients were then randomly assigned to fortnightly treatment periods with Pancrex V Forte, Creon, and Pancreatin Merck. The dose of pancreatic extract was so adjusted that during each treatment fortnight the daily lipase content was identical to that received when on treatment with Pancrease.

Stools were collected over 48 hours at the end of weeks 1, 3, 5, and 7. Faecal fat content was measured using the method already described and faecal nitrogen using a Tecator Kjeltec Auto Model 1030 nitrogen analyser. This timing of collection was chosen to minimise disturbance to schooling and work. The daily output of faecal fat and nitrogen was calculated from the 48 hour faecal collection.

Throughout the investigation the patients recorded daily their subjective symptoms (on a scale of 1-3) for abdominal distension, stool odour, stool consistency, and also the number of bowel actions each day. For the purpose of analysis, the symptom scores were taken from the second week of treatment when the patients were on a constant fat diet. Some patients were not able to tolerate one particular preparation and in these cases the weekly symptom score was estimated from the daily scores available before stopping that preparation. At the end of the study each patient was asked for their own individual preference of pancreatic extract. All results are expressed as median (range).

Statistical analysis was undertaken using Wilcoxon’s rank sum test and Student’s paired t test where appropriate. Consent for this study was given by the local ethical committee.

Results

Six patients were unable to tolerate the Pancrex V Forte because of untoward gastrointestinal symptoms of steatorrhoea, and in five of these patients faeces were not collected as the patients were not on the constant fat diet; thus there were only 14 faecal fat and nitrogen estimations in the children taking Pancrex V Forte. There was excellent dietary
recording by the patients with very little variation in dietary fat intake in each study period.

**Weekly symptom score.** (Fig. 2). There was no difference in the weekly symptom score when on Pancrease (38 (22–57)) and on Creon (40 (9–54)), but both were significantly lower (p<0.01) than the symptom scores for Pancreatin Merck (55 (20–75)) and Pancrex V Forte (62 (40–78)). There was no significant difference for the scores between Pancrex V Forte and Pancreatin Merck.

**Fat absorption.** (Fig. 3). There was no difference in the per cent fat absorption between Pancrease (87 (24–95)) and Creon (85 (56–94)), but both were significantly higher, however, than Pancrex V Forte (74 (52–93)) (p<0.01), and Pancrease was significantly higher than Pancreatin Merck (81 (34–94)) (p<0.05). There was no significant difference between Pancrex V Forte and Pancreatin Merck nor between Pancreatin Merck and Creon.

**Faecal nitrogen.** (Fig. 4). There was no significant difference in the faecal nitrogen content between Creon (2.1 (0.6–4.4) g/day) and Pancrease (1.6 (0.5–8.6) g/day) and between Pancrex V Forte (2.9 (0.4–5.4) g/day) and Pancreatin Merck (2.7 (1.0–

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**Fig. 3** Fat absorption, as derived from (dietary fat–faecal fat)/dietary fat×100%, in patients with cystic fibrosis treated with four pancreatic extracts. The horizontal bar represents the median value.

**Fig. 2** Weekly symptom scores for patients with cystic fibrosis treated with four pancreatic extracts. The horizontal bar represents the median value. Open circles represent six patients unable to tolerate Pancrex V Forte because of undue symptoms.

**Fig. 4** Faecal nitrogen content (g/day) in patients with cystic fibrosis treated with four pancreatic extracts. The horizontal bar represents the median value.
7-6) g/day). The only difference noted was that both Creon and Pancrease were significantly lower than Pancreatin Merck (p<0.05).

On subjective questioning, eight children preferred Pancrease as it was the preparation they were accustomed to using, 10 children preferred Creon as it was equally efficacious as Pancrease but fewer capsules had to be taken, and one preferred Pancrease V Forte as he liked the taste. No patient stated a preference for Pancreatin Merck.

**Discussion**

In this study we have confirmed the benefits of the microsphere system of pancreatic extract. Previous reports have already shown the superiority of Pancrease over conventional preparations.\(^6\) Clinical evidence of the effect of Creon has to date only appeared in German publications.\(^10\) This study shows that patients on Creon and Pancrease had fewer gastrointestinal symptoms than patients on Pancrease V Forte and Pancreatin Merck. Fat absorption was significantly improved with Creon and Pancrease compared with Pancreatin V Forte, and also the fat absorption with Pancrease was superior to that with Pancreatin Merck, although Pancreatin Merck and Creon were similar. Faecal nitrogen content was less with both Creon and Pancrease compared with Pancreatin Merck. When taking either Creon or Pancrease children with cystic fibrosis were able to enjoy a normal diet without any dietary fat restrictions. Moreover, dietary fat absorption was well over 80% in most patients and 90% in one third of the children, reflecting the high efficiency of these two products. Our results with Pancreatin Merck were less satisfactory than with Creon or Pancrease and were similar to Pancrease V Forte. Pancreatin Merck is of similar formulation to Creon and Pancrease.

Creon and Pancrease have revolutionised the dietary management of patients with cystic fibrosis. It has been recognised that a greater benefit is obtained from the diet in children with cystic fibrosis than in adults.\(^12\) Hyperalimentation in children with cystic fibrosis has been shown to be associated with improvement in pulmonary function.\(^15\) Fat as a major energy source in the diet is now readily available to children with cystic fibrosis since the availability of more effective pancreatic supplements. Optimum nutrition, without dietary restriction, is thus possible in the child with cystic fibrosis.

There are other advantages of the microsphere system preparations. All but one patient preferred the taste of the new preparations and because of their increased efficiency the children found that fewer capsules were required to control gastrointestinal symptoms. Many patients reported a greater sense of 'well being' with Pancrease and Creon because of lack of symptoms. Several children preferred Creon to Pancrease because the increased enzyme content of Creon meant that they took fewer capsules. Comparative costs showed that in this study Creon was 40% cheaper than Pancrease, though both products were four to seven times more expensive than Pancrex V Forte. It must be remembered, however, that on the dose of Pancrex V Forte used in this study six patients had uncontrollable symptoms and dietary malabsorption was common; thus a larger dose of Pancrex V Forte would be necessary to control symptoms, with the possible dangers of hyperuricaemic and hyperuricosuria.\(^17\)

On such a larger dose of Pancrex V Forte the price differential between Pancrex V Forte and Creon and Pancrease would not be so pronounced.

We conclude that both Creon and Pancrease are equally effective in correcting and controlling the symptoms of pancreatic insufficiency in children with cystic fibrosis. We believe that one or other of these two products is currently the treatment of choice when pancreatic supplementation is used.

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**References**


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