

# Enteric coated microspheres of pancreatin in the treatment of cystic fibrosis: comparison with a standard enteric coated preparation

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**ABSTRACT** In an open, randomised crossover study enteric coated microspheres of pancreatin were compared with a standard preparation of enteric coated pancreatin over two consecutive 28 day treatment periods in 23 adults with steatorrhoea due to cystic fibrosis. Lipase intake was equal to the patients' previous requirements and was the same during the two months. Patients performed 72 hour faecal collections at the end of each month and completed diary cards daily throughout. Comparison of the month of treatment with enteric coated microspheres with the month of standard enteric coated tablets showed a significant increase in body weight on microsphere capsules ( $p < 0.02$ ). There was also a reduced frequency of bowel actions ( $p < 0.001$ ) and abdominal pain ( $p < 0.05$ ), and improvement in stool character ( $p < 0.001$ ) on microsphere capsules. Faecal fat excretion was reduced by 44% with the microsphere capsules ( $p < 0.01$ ), and 86% of patients showed an increased coefficient of fat absorption (mean increase 13%, 95% confidence limits 6.5-19.1%;  $p < 0.001$ ). Eighty one per cent of patients preferred microsphere capsules of the two treatments. Thus enteric coated microsphere capsules are more effective in treating steatorrhoea in cystic fibrosis than standard enteric coated tablets.

About 95% of adults with cystic fibrosis have steatorrhoea due to exocrine pancreatic insufficiency,<sup>1</sup> which is often severe.<sup>2</sup> Malabsorption therefore contributes to the very high incidence of undernutrition in these patients, which is in turn related to the severity of pulmonary disease, and also to morbidity and mortality.<sup>3</sup> Furthermore, there is preliminary evidence that improving nutrition in patients with cystic fibrosis can produce sustained improvements in respiratory function.<sup>4</sup> Treatment with pancreatin may reduce fat excretion but rarely to within the normal range,<sup>2</sup> largely owing to inactivation of enzyme supplements by low intraluminal pH.<sup>5</sup> For this reason enteric coated preparations of pancreatin, designed to dissolve above pH 5 in the duodenum, are commonly prescribed in Britain, but

there is doubt about whether they are generally more effective.<sup>6</sup> They may fail to dissolve because of low intraduodenal pH, or may be retained by the pylorus.<sup>7</sup> Formulations designed to avoid this latter problem, consisting of enteric coated microspheres of pancreatin contained in a gelatin capsule (microsphere capsules) have recently been developed,<sup>8</sup> but this type of preparation has not been compared with standard enteric coated pancreatin tablets (standard tablets), and this was the aim of the present study.

## Patients and methods

### PATIENTS

Twenty three patients (11 of them male) with cystic fibrosis attending the Brompton Hospital adolescent and adult cystic fibrosis clinic entered the study. Their mean (SD) age was 24.8 (4.2) years. In each the sweat sodium concentration was  $> 70$  mmol (mEq)/l and they all had typical pulmonary disease. They also had evidence of exocrine pancreatic insufficiency, with symptomatic steatorrhoea responsive to pancreatin,

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and were taking standard enteric coated tablets (Pancrex V Forte) with meals, the mean dosage being 30 (17.3) tablets a day. The patients had each previously adjusted the daily dose of standard tablets, which was stable at the time of the study, to give optimum control of their steatorrhoea, although in general they had some symptomatic evidence of persistent fat malabsorption. None of the patients was taking antacids or histamine<sub>2</sub> receptor antagonists. Five patients had abnormal results in biochemical tests of liver function, and two of these had splenomegaly. Two had diabetes mellitus controlled by insulin, and in other respects the patients were clinically stable. Informed consent was obtained from the subjects, who were studied at an outpatient clinic held in the afternoon.

#### METHODS

We used an open, randomised crossover design with two consecutive 28 day treatment periods, consisting of standard enteric coated tablets (Pancrex V Forte tablets) and enteric coated microsphere capsules (Creon capsules) respectively. On entry to the study each patient's daily dosage regimen of standard tablets was ascertained. After randomisation patients were prescribed either their usual regimen of standard tablets or microsphere capsules in a ratio of 0.7 capsules for each standard tablet. Since the ratio of declared lipase content (BP units) of Pancrex V Forte tablets to Creon capsules is 0.7:1 (*British National Formulary* 1986), this ensured that lipase intake during the two months of the study would be similar in individual patients. The equivalent ratio for free protease (BP units) of Pancrex V Forte to Creon is 1.6:1, and consequently the ratio of monthly intake was 2.2:1.

Patients were assessed in the clinic on entry to the study, at crossover, and on completion. At each visit their weight was recorded in underclothing, scales calibrated to  $\pm 0.1$  kg being used.

Throughout the study patients completed diary cards daily, and recorded the following information: (a) the number of standard tablets or microsphere capsules consumed; (b) their appetite, on the basis of a scoring system of 1 representing "very good" to 4 representing "poor;" (c) the number of their bowel actions; (d) the character of their stool (score: 1—"formed," 2—"semi-formed," and 3—"loose"); (e) whether the stool floated in the pan ("Yes" or "No"); (f) whether they had experienced abdominal pain that day ("Yes" or "No").

The patients' daily dietary intakes were assessed by one of us (IS) and they were instructed to continue as before with their normal diet, keeping fat intake constant throughout the study. None of the patients was using medium chain triglyceride oil. They were

also instructed to complete daily food record charts for the final five days of each month, and a system of "fat exchanges" was used to ensure that fat intake in particular would be similar during these two five day periods. Total fat intake was calculated for the middle three of the five days monitored and total lipase intake from enzyme supplements for these days was calculated from the diary cards.

Patients were issued with containers and were instructed to make a 72 hour faecal collection over the final three days of each month—that is, to start on the third day of dietary recording. The collections were frozen at  $-20^{\circ}\text{C}$  until the analysis. Stool weight was recorded and faecal fat content measured by a modification of the van de Kamer technique.<sup>9</sup> In each case the results were expressed as the mean daily value. The upper limit of normal for faecal fat excretion in our laboratory is 5 g/day. The coefficient of fat absorption for the three days was calculated with the following formula:

$$\frac{(\text{Fat intake (g)} - \text{fat excretion (g)})}{\text{Fat intake (g)}} \times 100.$$

So far as possible the patients' other treatment remained unchanged during the study. At the end of the study the patients were asked to state which treatment period they had preferred and to give their reasons.

#### STATISTICAL ANALYSIS

The data were analysed by the method of Hills and Armitage.<sup>10</sup> The treatment and period effects were calculated and the data were tested for the presence of a treatment-period interaction. Comparisons were made by means of Student's *t* test and probabilities of over 5% were considered non-significant.

#### Results

One patient who was unable to swallow microsphere capsules was withdrawn from the study. Data from a second patient were not analysed as he inadvertently took considerably more lipase during one month than during the other. Thus data on 21 patients remained for analysis. There was evidence of treatment-period interaction in relation to appetite score ( $p < 0.05$ ) but not with any of the other variables. There was evidence of a period effect only in relation to bowel frequency (mean effect 0.35/day;  $p < 0.05$ ).

Analysis of the diary cards showed that the mean (SD) daily number of microsphere capsules and standard tablets taken during the two months was 19.0 (12.1) and 27.6 (16.3) respectively. Mean daily lipase intake during the month of microsphere capsules,  $152.3 (96.6) \times 10^3$  BP units, was therefore very similar to that during the month of standard tablets,  $154.8$

(91.4)  $\times 10^3$  BP units, and in 19 patients intake while taking microsphere capsules was within 20% of that while they took standard tablets. The mean body weight of the patients on entry to the study was 50.2 (9.8) kg. There was a mean increase in body weight of 0.90 kg during the month of microsphere capsules, which was significantly greater ( $p < 0.02$ ) than the increase of 0.01 kg recorded during the month of standard tablets (table 1). There was a highly significantly lower frequency of bowel actions during the month of microsphere capsules than during the month when standard tablets were taken ( $p < 0.001$ ), and also improvements in stool character ( $p < 0.001$ ) and "buoyancy" ( $p < 0.01$ ). Abdominal pain occurred less frequently during the month of microsphere capsules ( $p < 0.05$ ). Because of the treatment-period interaction, mean appetite score was analysed for the first month only and there was no significant difference between the two preparations (Student's *t* test)—2.20 (0.61) for the patients having microsphere capsules and 1.76 (0.50) for those having standard tablets.

Mean daily dietary fat intake for the three days relating to the faecal collections was similar during the two treatments, being 96.7 (27.0) g with microsphere capsules and 98.5 (36.7) g with standard tablets. Mean daily lipase intake was also similar, being 153.1 (99.2)  $\times 10^3$  BP units with microsphere capsules and 159.6 (97.2)  $\times 10^3$  BP units with standard tablets. Intake of fat and lipase during the month of microsphere capsules was within 20% of that during the month of standard tablets in 18 of the

21 patients. Comparison of the microsphere capsule month with the standard tablet month showed that stool weight was reduced during the microsphere capsule month ( $p < 0.01$ ) (table 2). In no patient was faecal fat excretion normal on either regimen, but in five patients it was less than 10 g/day with microsphere capsules, whereas only two patients were below this value with standard tablets. There was a difference between the two treatments in the means of faecal fat excretion of 11.9 g/day ( $p < 0.01$ ), representing a 44% reduction during microsphere capsule treatment. The coefficient of fat absorption was also greater with microsphere capsules than with standard tablets ( $p < 0.001$ ), and this was so in 18 of the 21 patients (86%).

Seventeen of the 21 patients (81%) expressed a preference for microsphere capsules, reduction in stool frequency and improvement in stool character being the most common reasons given. Four patients had no preference but two of them opted to continue with microsphere capsules. No patient preferred standard tablets.

## Discussion

Malabsorption in cystic fibrosis is difficult to treat, largely owing to the presence of low intraluminal pH. The use of cimetidine before meals in addition to pancreatin is therefore logical<sup>11</sup> but inconvenient. Alternatively, pancreatin may be contained in a pH sensitive "enteric coating," but this may cause the tablets to be retained in the stomach<sup>7</sup> and may delay

Table 1 Changes in body weight and daily recordings obtained from diary cards

	ECMP	SECP	Treatment difference (ECMP—SECP)	95% confidence limits	<i>p</i>
Weight change (kg)	+0.90	+0.01	+0.89	+0.21 to 1.56	<0.02
Bowel actions	1.71	2.37	-0.67	-0.99 to -0.35	<0.001
Stool character*	1.33	1.72	-0.39	-0.53 to -0.25	<0.001
Stool "buoyancy" (% days when stool floated)	35.9	60.2	-24.3	-40.0 to -8.6	<0.01
Abdominal pain (% days when present)	6.0	12.6	-6.6	-12.1 to -1.2	<0.05

\*Score: from 1—"formed" to 3—"loose."

ECMP—enteric coated microsphere capsule preparation of pancreatin; SECP—standard enteric coated tablet preparation of pancreatin.

Table 2 Data relating to faecal collections

	ECMP	SECP	Treatment difference (ECMP—SECP)	95% confidence limits	<i>p</i>
Faecal weight (g/day)	248.0	328.1	-80.1	-128.9 to -31.3	<0.01
Faecal fat (g/day)	15.2	27.1	-11.9	-18.3 to -5.5	<0.01
Coefficient of fat absorption (%)	83.4	70.6	+12.8	6.5 to 19.1	<0.001

ECMP—enteric coated microsphere capsule preparation of pancreatin; SECP—standard enteric coated tablet preparation of pancreatin.

dissolution.<sup>12</sup> Enteric coated preparations appear advantageous, however, in patients with particularly low intragastric pH,<sup>13</sup> a feature of cystic fibrosis,<sup>14</sup> though they do not usually abolish steatorrhoea.<sup>15</sup> Standard tablets are widely used in Britain and appear advantageous in many patients with cystic fibrosis.

Enteric coated microsphere capsules are designed to avoid the problem of pyloric retention and to be dispersed more rapidly in the chyme. Studies of microsphere capsules directed at fat balances in patients with cystic fibrosis indicate that they are a more effective form of treatment than non-enteric coated pancreatin.<sup>8 16-18</sup> The formulation (Pancrease) may reduce faecal fat excretion to near normal levels,<sup>8</sup> though doses larger than those recommended by the manufacturer are often required. Creon, the preparation used in the present trial, has been less widely studied<sup>19-23</sup> and only one study has examined patients with cystic fibrosis,<sup>19</sup> the others being concerned with patients with other causes of exocrine pancreatic insufficiency. These studies suggest that this enteric coated microsphere preparation may also be more effective than non-enteric coated pancreatin.

Enteric coated microsphere capsules seem not to have been compared with standard enteric coated tablets. We considered it important to compare a dose of lipase contained in standard tablets that apparently gave reasonable control of steatorrhoea with an equal dose in the new formulation, since this is the most practical means of assessing therapeutic benefit in individuals. It also appears that this form of comparison has not been made with microsphere capsules.

Our results show that, compared with standard tablets, microsphere capsules of pancreatin produced clear subjective and objective evidence of reduction in steatorrhoea, including a 44% fall in faecal fat excretion. This is important since the symptoms of malabsorption may be a considerable psychosocial problem in cystic fibrosis and since distal intestinal obstruction syndrome, a serious complication of the disease, seems to be related to poor control of steatorrhoea.<sup>24</sup> Furthermore, 95% confidence limits suggests that in our patients use of microsphere capsules would save 50-165 kcal of energy a day in reduced fat excretion, apart from possible improvements in absorption of other nutrients. Most importantly, there was a significant increase in body weight with microsphere capsules compared with standard tablets, despite the relatively short study period. Diets low in fat were previously advocated for control of steatorrhoea in cystic fibrosis, but this resulted in reduced intake of calories, essential fatty acids, and fat soluble vitamins in patients already

deficient in these.<sup>25</sup> To improve nutrition and life-style, relatively normal diets with a calorie intake above the recommended daily allowance and a concomitantly normal to high intake of fat are now recommended. Optimum control of steatorrhoea is equally important and the weight gain we found indicates a clinically significant advantage in microsphere capsules over standard tablets in this respect. Our findings are based on the assumption that patient compliance was good and, to judge by the high standard to which the diary cards were completed, we feel this is justified. Furthermore, poor compliance with the faecal collections would presumably have reduced the difference between the two treatments.

The major disadvantage of enteric coated microsphere preparations is their cost, in that Creon is over four times more expensive per unit than Pancrex V Forte (basic NHS price, *MIMS* December 1986). The overall difference is less, however, since patients will need fewer units of microsphere capsules than of standard tablets. The need for expensive and invasive supplementary nutrition may be reduced, together with the number of hospital admissions for distal intestinal obstruction syndrome. It is hoped that the ensuing improvement in nutrition will also have a beneficial effect on pulmonary function.

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