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Efficacy of oral pancreatic enzyme therapy for the treatment of fat malabsorption in HIV-infected patients

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SUMMARY

Background: Nutrient malabsorption is a negative prognostic factor in acquired immunodeficiency syndrome and recent studies have shown that pancreatic insufficiency is a codetermining factor of malabsorption.

Aims: To evaluate the effectiveness of open-label oral pancreatic enzyme supplementation therapy in acquired immunodeficiency syndrome patients with fat malabsorption.

Patients and methods: Twenty-four consecutive patients with human immunodeficiency virus infection and fat malabsorption were recruited (11 males, 13 females; median age, 9.1 years). Faecal fat loss was evaluated by steatocrit assay at entry to the study (T-0), after 2 weeks (T-1) without pancreatic enzyme treatment and after a further 2 weeks (T-2) of treatment with pancreatic extracts (Creon 10 000 at a dose of 1000 units of lipase per gram of ingested dietary fat). Faecal elastase-1 and chymotrypsin were assayed at entry.

Results: Six patients (25%) had abnormally low elastase-1 and/or chymotrypsin faecal concentration. In all patients, steatocrit values were elevated at both T-0 and T-1. Five patients proved intolerant to pancreatic enzyme treatment because of the onset of abdominal pain, and therapy was discontinued. In the 19 patients who concluded the study, steatocrit values during pancreatic enzyme treatment (T-2) were significantly lower than at entry ($P < 0.0001$). At T-2, in eight of 19 patients, steatocrit values were within the normal limit and the frequency of cases cured or improved on pancreatic enzyme therapy (at T-2) was significantly higher than that observed during the previous study period without enzyme treatment (T-1) ($P < 0.01$). A positive significant correlation was found between steatocrit values at entry and the Centers for Disease Control class ($P < 0.0005$); also, the decrease in steatocrit values during pancreatic enzyme therapy (difference between steatocrit value at T-2 and steatocrit value at T-0) positively correlated with the Centers for Disease Control class ($P < 0.05$).

Conclusions: This pilot, open-label study showed that pancreatic enzyme supplementation therapy is highly effective in reducing faecal fat loss in human immunodeficiency virus-infected patients with nutrient malabsorption. Further double-blind studies must be undertaken to verify these results and, if they are confirmed, pancreatic enzymes can be added to our weapons in the fight against human immunodeficiency virus-associated nutrient malabsorption.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a pandemic disease which affects an estimated 40 million people world-wide.[1] Although the improved strategies of antiretroviral therapy have reduced morbidity,[2] the

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prognosis of patients with human immunodeficiency virus (HIV) infection remains unfavourable. A major negative prognostic factor in AIDS is the onset of nutrient malabsorption which contributes to malnutrition. Several studies have underlined the important role of intestinal damage in determining protein loss and increased intestinal permeability.[3–6] However, our recent studies have demonstrated that pancreatic insufficiency is quite frequent in both children[7] and adults[8] with AIDS, and a significant negative correlation was found between the degree of steatorrhoea and the faecal concentration of the pancreatic enzymes.[7] Consequently, pancreatic insufficiency plays a role in determining nutrient malabsorption in AIDS. Therefore, it could be hypothesized that treatment with pancreatic extracts should improve nutrient absorption in AIDS patients with malabsorption syndrome. However, to date, no studies have been performed to consider this possibility.

As the first phase of testing this hypothesis, we have evaluated the effect of 2 weeks of open-label oral pancreatic enzyme supplementation therapy on faecal fat excretion in HIV-infected patients with fat malabsorption.

PATIENTS

From a total of 85 patients examined at the out-patients clinics of two tertiary care centres for paediatric HIV infection, between October 1997 and March 1998, we recruited all consecutive subjects with steatorrhoea. In this way, 24 children (11 males, 13 females; median age, 9.1 years; range, 1–14 years) were enrolled. At the time of the study, none of the patients were receiving the highly active antiretroviral combination therapy,[2] as the protocol was begun before the routine introduction of this treatment. The following information was obtained for each child: (a) HIV class according to the Center for Disease Control (CDC) criteria;[9] (b) CD4 lymphocyte count; (c) patient's weight expressed as weight Z-score; (d) presence of opportunistic infections; (e) drug treatment, including zidovudine, dideoxydanosine, cotrimoxazole and pentamidine; (f) presence of diarrhoea (defined as three or more unformed or liquid stools per day). The weight Z-score was calculated as follows: Z-score = (observed weight – mean weight for sex and age)/standard deviation for sex and age; as in our previous study,[10] Italian regional standards were used as reference values.

Out-patient subjects without steatorrhoea at the time of the first evaluation were not included in the study or investigated further.

Informed consent was obtained from the parents or the legal guardians of the children.

The study protocol was approved by the Ethics Committee of the University Hospital.

STUDY DESIGN

All the consecutive patients with steatorrhoea underwent a pre-study assessment within 1 week before the study started; they were put on a standard diet and, after 1 week, steatorrhoea determination and faecal pancreatic function tests were performed (time T-0). All the patients with confirmed steatorrhoea at this time continued to be studied, regardless of the pancreatic function test results. Steatorrhoea was then re-evaluated after 2 weeks without pancreatic enzyme therapy (time T-1). Finally, pancreatic supplementation treatment was started and, 4 weeks after the beginning of the study (2 weeks after the beginning of treatment), steatorrhoea was again evaluated (time T-2).

The pancreatic supplementation therapy administered was Creon 10 000 at a dose of 1000 units of lipase per gram of ingested dietary fat. The declared enzyme activity units (unit of the Fédération Internationale Pharmaceutique) per capsule of Creon were as follows: lipase, 10 000 U; amylase, 8000 U; protease, 600 U. Between four and nine pancreatic enzyme capsules were consumed daily, according to the different dietary fat intakes of each patient. Pill counts were performed halfway through the study and at the end.

During the various study periods, the patients maintained a standard diet containing approximately 2 g of fat/kg body weight. A dietary chart containing a list of different foods with the relative fat contents was given to patients' parents and they were instructed to fill in the dietary chart every day with the aid of dieticians. Furthermore, the parents were able to contact the reference centres whenever necessary, and frequent telephone contacts helped to ensure adherence to the therapy and diet.

Definition of response

During pancreatic enzyme therapy, a full response to treatment was defined as normalization of steatocrit in a

subject with baseline elevated values; a partial response was defined as a reduction in steatocrit values below baseline, but without achieving normalization; a lack of response was defined as evidence of steatocrit values equal to or higher than at baseline.

Evaluation of side-effects

During the 4-week study period, the parents recorded any clinical symptoms and the patients were re-examined in hospital for any adverse reactions at the end of the study. Drug administration was stopped when a clinical reaction occurred. Complete blood count and serum chemistry panel were assayed both at baseline and at the end of the study, following pancreatic enzyme supplementation therapy.

METHODS

Stools were collected over 24 h from children receiving a standard diet (carbohydrates 50–60% of total calories, proteins 12–15% and fats approximately 30%); they were subsequently homogenized, weighed and stored at −20 °C. An aliquot was used to determine faecal enzymes in the Division of Internal Medicine laboratory of the University of Palermo. Another aliquot was used to determine lipid faecal concentration in the Department of Paediatrics laboratory of the University of Naples.

Steatorrhoea determination

Faecal fat excretion was quantitatively estimated by the steatocrit method, as previously reported.[11] In brief, 0.5 g stools were further homogenized with 0.06 g sand and 2 volumes water, and 70 μL was introduced into a microhaematocrit tube, which was sealed with wax and centrifuged for 15 min at 12 000 rev/min. After centrifugation, a lower layer composed of non-fatty faecal solids (S) and a liquid intermediate layer were invariably present. In patients with steatorrhoea, the tubes showed three different layers, as a third upper fatty layer (F) was evident. Steatocrit was expressed as a percentage using the following formula: Steatocrit = $F/(S + F) \times 100$. The upper limit for normal steatocrit values was selected as 2%, as this is the highest value observed in our laboratory for healthy subjects in the age range considered.[11] It has been previously shown that the mean interday coefficient of variation can be as low as 2% and does not exceed 20%;[12] therefore, the 24-h steatocrit can be regarded as having a narrow variability range.

Pancreatic function tests

Pancreatic function was investigated by two distinct non-invasive tests: the quantitative determinations of elastase-1 concentration and chymotrypsin activity in faecal specimens. Elastase-1 concentration was determined by a commercially available enzyme-linked immunoabsorbent assay test, which uses two monoclonal antibodies against two distinct specific epitopes of human pancreatic elastase (Schebo-tech, Wettenberg, Germany). Results were expressed as μg/g of stools or as μg/24 h. The lower normal limit of elastase-1 was 200 μg/g of stools or 10 000 μg/24 h.[7, 8, 13] Chymotrypsin activity was determined at 37 °C by a photometric assay (Monotest Chymotrypsin, Boehringer, Mannheim, Germany). Results were expressed as U/g of stools or as U/24 h. The lower normal limit was 7.5 U/g or 375 U/24 h. The cut-off limits were derived from data obtained in the same laboratory in 300 age-matched healthy controls.[14] Both elastase-1 and chymotrypsin activities were determined on specimens kept frozen for up to 30 days. Previous data showed that cold storage did not modify the results, the interassay coefficient of variation being 9.8% for chymotrypsin and 8.3% for elastase-1.

STATISTICAL ANALYSIS

Student's *t*-test for paired data was used to compare the steatocrit values recorded at the pre-study assessment (T-0), during the wash-out period (T-1) and during pancreatic enzyme treatment (T-2). Fisher's exact test was used to compare the frequency of cases showing normal steatocrit values with and without pancreatic supplementation therapy. The chi-squared test for trend was used to compare the frequency of cases showing cured, improved or unchanged fat malabsorption with and without pancreatic enzyme supplementation therapy. The response rate to treatment was calculated based on an intention-to-treat 24 patients.

Spearman's correlation coefficient r was applied to determine the significance of the correlation between baseline steatocrit values (steatocrit at T-0) and the modifications in steatocrit values during the different phases of the study (steatocrit values at T-2 – steatocrit

values at T-0) vs. CDC class, weight Z-score and CD4 count.

RESULTS

The 24 children enrolled were classified according to their HIV infection state as follows: 9 C3, 1 C2, 1 C1, 6 B3, 3 B2, 2 A3, 2 A2.

All the recruited patients had confirmed elevated steatocrit values at the pre-study assessment (T-0). Furthermore, with regard to the pancreatic function tests, six patients (25%) had abnormally low elastase-1 and/or chymotrypsin faecal concentration. Of these six children, three had isolated elastase-1 deficiency, one isolated chymotrypsin deficiency and two deficiency in both pancreatic enzymes. Diarrhoea was observed in 14 children.

After the first 2 weeks of the study period (T-1), without any pancreatic supplementation therapy, the patients underwent another 24-h stool collection to determine steatocrit values: all were confirmed as having steatorrhoea as none had a normal steatocrit and values were not different from the baseline assessment (T-0) (Table 1).

Thus, they were started on pancreatic enzyme therapy. However, in five of the 24 patients, treatment was withdrawn due to the onset of abdominal pain. This appeared within the first 2–5 days of treatment and disappeared within 24 h after drug withdrawal, indicating a close relationship with pancreatic enzyme therapy. Nineteen patients completed the study and underwent a third steatocrit determination, after 2 weeks of pancreatic enzyme therapy. At this time (T-2), steatocrit was normal in eight of 19 patients and, in the whole study group, the mean steatocrit value was significantly lower than at the two previous determinations ($P < 0.0001$) (Table 1). In each patient who completed the study, steatocrit values were lower during pancreatic enzyme treatment than at the two previous determinations (Figure 1).

Table 1. Mean steatocrit values ± s.d. (%) and number of cases with normal steatocrit in the 19 HIV-infected patients who completed the study, at entry to the study (T-0), after 2 weeks without pancreatic enzyme therapy (T-1) and after 2 weeks of treatment with pancreatic extracts (T-2)

	T-0	T-1	T-2
Steatocrit value	7.4 ± 2.6*	7.3 ± 3.7*	3.9 ± 2.1*
Number of cases with normal steatocrit values	0/19	0/19	8/19

Five of the 24 patients originally included did not complete the study due to intolerance to pancreatic enzyme treatment (see Results section).

*T-0 vs. T-1, not significant; T-0 vs. T-2, $P < 0.0001$ ($t = 7.406$; Student's *t*-test for paired data); T-1 vs. T-2, $P < 0.0001$ ($t = 7.158$; Student's *t*-test for paired data).

Table 2 shows the response rate of pancreatic enzyme therapy in comparison with the time of entry to the study, considering all the 24 patients initially included in the study. On pancreatic extracts, steatorrhoea decreased in 11 of 24 subjects and disappeared in eight of 24 subjects. In contrast, the comparison between baseline data and those obtained after the first 2 weeks of the study (during which no enzymatic treatment was given) showed that steatorrhoea did not completely regress in any of the patients at this stage. Statistical analysis showed that the frequency of cases cured or improved on pancreatic enzyme therapy (at T-2) was significantly higher than that observed during the previous study period without enzyme treatment (T-1) ($P < 0.01$; chi-squared test for trend = 6.63). The frequency of normal steatocrit results was significantly higher during pancreatic enzyme treatment than in the previous period (8/24 cases vs. 0/24; $P < 0.005$; Fisher's test).

A positive significant correlation was detected between steatocrit values at entry and the CDC class (Spearman's coefficient *r*: $r = 0.60$; $P < 0.0005$) (Figure 2). Also, the decrease in steatocrit values during pancreatic enzyme therapy (difference between steatocrit value at T-2 and steatocrit value at T-0) positively correlated with the CDC class (Spearman's coefficient *r*: $r = 0.38$; $P = 0.05$). No significant correlation was found between steatocrit values at baseline and steatocrit decrease during pancreatic enzyme therapy and CD4+ count or weight Z-score.

All of the six patients who had low elastase-1 and/or chymotrypsin values at entry to the study completed the protocol: on pancreatic enzyme treatment, three patients normalized and the other three had lower steatocrit values than during the previous study phases.

Twelve of the 14 patients with diarrhoea at entry to the study completed the protocol: diarrhoea disappeared in only three during pancreatic enzyme treatment, whereas in the other nine it persisted.

During the whole study period, patients were in a stable clinical condition and there was no modification

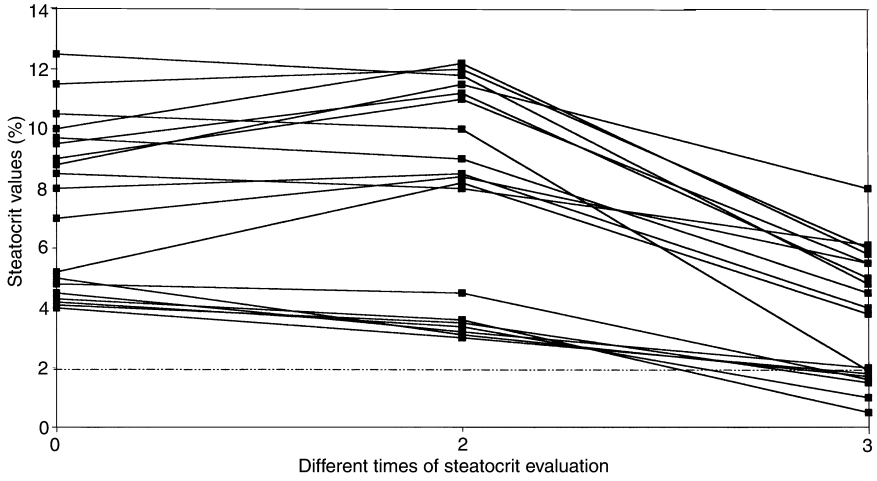

Figure 1. Individual steatocrit values recorded at each of the three study times: 1, baseline evaluation at entry to the study; 2, second evaluation, without pancreatic enzyme treatment; 3, third evaluation on oral pancreatic enzyme treatment. Dotted line, high normal limit. Five of the 24 patients originally included did not complete the study due to intolerance to pancreatic enzyme treatment (see Results section).

in the long-term therapy (antiretroviral therapy, antibiotics, etc.). There was no difference in the incidence of opportunistic infections.

Daily dietary fat intake per kilogram of body weight was substantially identical during the two study periods (mean ± s.d. values: 2.2 ± 0.3 g/kg body weight at T-1; 2.3 ± 0.2 g/kg body weight at T-2).

No variations were observed in blood count and serum chemistry panel before and after pancreatic enzyme supplementation.

DISCUSSION

Two-thirds of patients with AIDS will have diarrhoea at some time during the course of their illness[15] and a large number will suffer from chronic diarrhoea and malabsorption syndrome.[3, 4] Nutrient malabsorption is certainly a major clinical problem as it contributes to malnutrition, thereby increasing the progression of HIV disease.[16] As a consequence, in HIV patients with nutrient malabsorption, any treatment which could reduce its severity is highly relevant. Although most of the studies on malabsorption syndrome in AIDS have underlined the role of intestinal mucosa damage,[3–6] more recently greater attention has been dedicated to the role of pancreatic impairment. Autopsy studies have shown severe pancreatic lesions in up to 90% of HIV-infected patients.[17, 18] Functional studies have demonstrated a high incidence of abnormalities in HIV-infected patients.[7, 8, 19] Overall, we have found steatorrhoea in 26% of consecutive HIV-infected children[7] and in 71% of adults.[8] Furthermore, abnormal pancreatic function tests were significantly associated with steatorrhoea.[7] It has been estimated that not less than 30% of patients have steatorrhoea because of pancreatic dysfunction.

These data suggested the opportunity of a trial with pancreatic enzyme therapy in AIDS. However, because oral pancreatic enzyme therapy represented a novel approach to treating nutrient malabsorption in HIV-infected patients and therefore implied a risk of poor tolerance, it was decided to undertake an unblind, open-label study to establish the safety of treatment and its

Table 2. Response rate (number of cases and percentage) of pancreatic enzyme therapy in comparison with the previous period during which no enzymatic treatment was given. All 24 patients initially included in the study were considered

	Lack of response	Partial response*	Complete response*
On pancreatic enzyme therapy	5/24† (19%)	11/24 (48%)	8/24 (33%)
Without pancreatic enzyme therapy	9/24 (39%)	15/24 (61%)	0/24 (0%)

Chi-squared test for trend = 6.63, $P < 0.01$.

*Complete response was defined as full normalization of steatocrit values; partial response was defined as a reduction in steatocrit values below baseline steatocrit values but still exceeding the normal limit (i.e. for 'pancreatic enzyme therapy period' T-2 vs. T-0; for 'pancreatic enzyme wash-out period' T-1 vs. T-0).

† The five patients with lack of response on pancreatic enzyme therapy were those who did not complete the study due to intolerance to pancreatic enzyme treatment (see Results section).

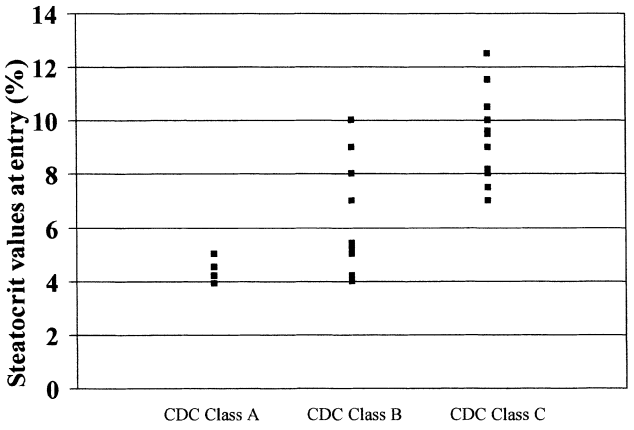

Figure 2. Relation between the steatocrit values at entry to the study and HIV clinical category (Center for Disease Control, CDC, classes). CDC class A, mild or no signs/symptoms; CDC class B, moderate signs/symptoms; CDC class C, severe signs/symptoms. Five of the 24 patients originally included did not complete the study due to intolerance to pancreatic enzyme treatment (see Results section).

efficacy as judged by fat absorption. The results indicate that supplementation therapy with pancreatic enzymes is able to reduce, or even completely abolish, fat malabsorption in HIV-infected patients. In fact, while on pancreatic enzyme treatment, steatorrhoea disappeared in one-third of patients originally included (8/24 cases) and steatocrit values fell in every subject who completed the study. Statistical analysis demonstrated that, during pancreatic supplementation therapy, steatocrit values were significantly lower than at entry. Obviously, this result could be extremely relevant if it is confirmed by further double-blind, placebo-controlled studies.

In this study, it was first shown that the severity of steatorrhoea and the subsequent improvement in fat absorption on enzyme treatment were related to more advanced HIV disease. In fact, both steatocrit values at entry and the decrease in steatocrit values on enzyme therapy significantly correlated with the CDC class (Figure 2), an index which evaluates the general condition of AIDS patients, taking into account clinical, immunological and nutritional status. Thus, the more severe the clinical condition, the more severe the steatorrhoea and the greater the improvement in fat absorption on pancreatic enzyme therapy.

However, some points deserve additional comments. First, this study fully confirms the lack of correspondence between the presence of steatorrhoea and diarrhoea in HIV-infected patients;[2, 4, 7] in fact, at entry, only 14 of the 24 patients showed diarrhoea. Furthermore, at the end of the study, although all patients benefitted from pancreatic treatment in terms of reduction in fat malabsorption, only in one-quarter of those with diarrhoea was this symptom cured. Thus, pancreatic supplementation therapy could be useful in reduced stool fat loss, but only in a minority of the patients was it able to cure the diarrhoea, which evidently has a multiple pathogenesis and is probably mainly dependent on intestinal mucosa damage.[4–6] Second, oral pancreatic enzymes can produce abdominal pain and 20% of the patients included in this study had to suspend the treatment. Although this side-effect was foreseeable, we had never observed it in previous trials in patients with coeliac disease[10] or cystic fibrosis.[20] Third, it is somehow surprising that the efficacy of supplementation therapy on steatorrhoea was not limited to patients with abnormal pancreatic function. It is possible that faecal elastase-1 and chymotrypsin determinations were not sensitive enough to reveal a mild degree of pancreatic dysfunction in AIDS patients, although it is an accepted concept that steatorrhoea due to pancreatic insufficiency is always associated with severe pancreatic insufficiency. It is conceivable that oral pancreatic enzymes modify the intestinal environment producing a direct effect against the overgrowth of bacteria in the duodenum and jejunum, with a consequent positive effect on intestinal absorptive capacity.

However, the beneficial effects of oral pancreatic enzyme therapy on fat absorption may be due to the natural course of the disease or be caused by a placebo effect of the treatment; in fact, it cannot be excluded that, during the course of the disease, there may have been a spontaneous remission of the fat malabsorption. Finally, it must be remembered that this study was carried out before the routine introduction of highly active antiretroviral therapy[2] which has been shown to significantly improve intestinal function in HIV-infected patients.[21] Thus, the effectiveness of pancreatic enzyme treatment must be re-evaluated, taking the new therapeutic strategies into account. However, in the 'new antiretroviral era', pancreatic enzyme treatment could be considered for the millions of people in the 'Third World' who do not have access to the new anti-HIV drugs.

In summary, this pilot, open-label study showed that: (a) pancreatic enzyme supplementation therapy is highly effective in reducing faecal fat loss in HIV-infected patients with nutrient malabsorption; (b) there

is a direct correlation between the clinical condition of the patients and the severity of steatorrhoea. Further double-blind studies must verify these results and, if they are confirmed, pancreatic enzymes can be added to our weapons in the fight against nutrient malabsorption in AIDS.

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