Controlled trial of oligopeptide versus amino acid diet in treatment of active Crohn's disease

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Abstract

Elemental diets are effective in inducing remission in active Crohn's disease, but how they exert this therapeutic effect is unclear. In a previous study a whole protein containing diet proved less effective than one in which food antigens were excluded, suggesting that exclusion of food antigens from the gut was a possible mechanism. This study was designed to test whether an oligopeptide diet of hydrolysed proteins was as effective as an amino acid based diet. These diets were equally antigen free but with different nitrogen sources. Forty four patients with active Crohn's disease were randomised in a controlled trial of amino acid versus oligopeptide diet. The feeds were given by nasogastric tube in equicaloric quantities and were the sole form of nutrition. Treatment was continued for four weeks although failure to improve by day 10 resulted in withdrawal. Quantitative leucocyte scintigraphy was used to investigate the effect of diet treatment on gut inflammation. Clinical and nutritional responses to treatment were also measured. Sixteen patients entered remission (including withdrawal of corticosteroids), six patients could not tolerate the nasogastric tube, and 22 patients failed to respond. The two diets were equally effective. Patients who responded had a rapid drop in clinical index of disease activity and a major reduction in the bowel uptake of leucocytes on scintigraphy. The oligopeptide and amino acid based enteral feeds were equally effective at inducing remission in active Crohn's disease. With both diets clinical improvement was accompanied by a reduction in intestinal inflammation.

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Keywords: Crohn's disease, amino acid diet, oligopeptide diet.

Figure 1: Study design. Active Crohn's disease was defined as symptomatically active disease with a CDAI >150 and at least one abnormal blood test indicative of activity. Remission criteria were a reduction in CDAI of 100 points or 40%, control of symptoms and withdrawal of all treatment including corticosteroids.

The mechanism by which formula diets can induce remission in active Crohn's disease and the choice of type of diet are controversial.^{1 2} Bowel rest, antigen removal, and improved nutrition may all contribute to the clinical response. A reduction in gastrointestinal protein loss, a decrease in intestinal permeability, and a reduction in faecal excretion of indium labelled leucocytes have all been shown,³⁻⁵ suggesting a direct effect of diet on inflammatory activity in the gut. In children, improved nutritional indices and improved growth can be achieved using an elemental diet.⁶⁻⁸ The remission induced by elemental diet is often longlasting and can be achieved in many patients with Crohn's disease who had been dependent on, or refractory to, corticosteroids.^{9 10}

Three different types of enteral or 'formula' feeds are available: amino acid based (elemental), protein hydrolysate (oligopeptide), and whole protein containing (polymeric). The different forms of nitrogen content have clear differences in the presentation of antigen to the intestinal mucosa. Whole protein containing diets present a range of dietary antigens, determined by the protein source, often milk protein. Oligopeptide based diets, made by protein hydrolysis, have a mean peptide chain length of four or five amino acids, which is too short for antigen recognition or presentation. Amino acid based diets, also known as chemically defined diets, are created by mixing of single amino acids and are entirely antigen free.

Four studies have compared amino acid and polymeric diets in Crohn's disease.¹¹⁻¹⁴ The studies differed in important aspects of their design, including the degree of malnutrition and whether corticosteroids were coadministered, and the results are conflicting. A survey among practising gastroenterologists has shown that the commonest current practice in the United Kingdom is to use an amino acid based feed.¹⁵ Both amino acid and oligopeptide based diets have been compared with corticosteroids in the treatment of active Crohn's disease. Three randomised controlled trials all showed amino acid diets to be as effective as corticosteroid treatment in achieving remission.¹⁶⁻¹⁸ Two randomised controlled trials have compared oligopeptide diet with drug treatment, using a combination of corticosteroids and sulphasalazine. In a small study in children both treatments seemed similar,⁷ but in a larger study in adults drug treatment was superior.¹⁹

This study was designed to test whether two diets, differing mainly in the form of dietary nitrogen, but both being antigen free, were

TABLE I Nutritional composition of E028 and Pepti-2000 LF Liquid

	E028	Pepti-2000 LF
Presentation	Dry powder 100 g packets made up to 500 ml	Liquid 500 ml bottles
Osmolality	500 mOsm/kg	470 mOsm/kg
Energy (kcal/100 ml)	80	100
Energy distribution (%)		
Protein equivalent	11	16
Fat	16	9
Carbohydrate	73	75
Nitrogen source	100% free synthetic amino acids	Protein hydrolysate of whey 15–20% free amino acids 75–80% short chain peptides Mean chain length 4.5
Fat (%)		
Saturates	17	58
Monounsaturates	56	11
Polyunsaturates	26	31
Carbohydrate	Maltodextrin	Maltodextrin
Emulsifier	Lecithin (E322) and Polysorbate (E433)	Mono and diacyltartaric acid esters of mono and diglycerides of fatty acids (E472(e))

equally effective in clinical use and in reducing intestinal inflammation. Patients with active Crohn's disease, ill enough to otherwise require corticosteroids, and with objective evidence of active inflammation were randomised to treatment with either amino acid or oligopeptide based diet. The two feeds were given in isocaloric quantities and were similar in composition, except that one contained oligopeptides from protein digestion and the other was a chemically defined amino acid based elemental diet. Assessment of response was made by leucocyte scintigraphy in addition to the Crohn's disease activity index (CDAI)²⁰ and laboratory measures of disease activity.

Patients and methods

Patients with Crohn's disease were considered for the trial if they satisfied all three of the following points: they had a least one symptom of active Crohn's disease, for example, diarrhoea, abdominal pain, anorexia, and weight loss; they had a CDAI²⁰ greater than 150, and they also had at least one abnormal laboratory measurement indicative of active disease. The laboratory measurements considered were haemoglobin concentration, male <12.5 g/dl, female <11.5 g/dl, platelet count >400 × 10⁹/l, erythrocyte sedimentation rate (ESR) >20 mm in the first hour, serum albumin <35 g/l,

C reactive protein (CRP) >4 mg/l, and α-1 acid glycoprotein (AAGP) >1.2 g/l.

Patients who fulfilled the entry criteria were offered a choice of entry into the trial or treatment with corticosteroids. Forty four patients agreed to participate in the study. Of these 19 were anaemic, 29 had raised platelet counts, 18 had raised ESR, 14 had low albumin, 23 had raised AAGP, and 25 raised CRP. Thirteen patients were receiving long-term prednisolone treatment with a mean daily dose of 14 mg (range 5–40 mg). The duration of previous corticosteroid treatment ranged from two months to 10 years (median 18 months). In all 13 patients previous attempts to withdraw corticosteroids had failed.

Figure 1 shows the study design. Patients were assessed at entry, at day 10, and weekly thereafter. Clinical disease activity was quantified by the CDAI and laboratory measures of activity (haemoglobin, platelet count, ESR, AAGP, and CRP). Total body weight, percentage of ideal body weight, and serum albumin concentration were used to assess the nutritional state. Thirty five patients were also assessed by technetium isotope hexamethylpropylene-amine-oxime (^{99m}Tc-HMPAO) labelled leucocyte scanning. The scintigraphic images of abnormal bowel uptake were quantified by computer aided image analysis with background subtraction,²¹ to produce a scan score reflecting the severity and extent of bowel inflammation. The pretreatment scan scores ranged from 6.7 to 380 (mean=97). A value of 20 has previously been defined as being the upper limit consistent with inactive disease.²² The one patient with a scan score below 20 (6.7) had extensive active colonic disease shown at colonoscopy immediately before entry into the trial. A repeat ^{99m}Tc-HMPAO scan was performed in 21 patients at the end of diet treatment to measure the change in gut inflammation in response to treatment.

After initial assessment the patients were randomised to one of the two treatment groups; 22 patients were treated with amino acid based 'Elemental 028' (E028, Scientific Hospital Supplies, Liverpool, UK) and 22 patients received the oligopeptide based diet 'Pepti-2000 LF liquid' (Cow and Gate, Trowbridge, Wiltshire, UK). Table I compares the nutritional composition of the two diets. Neither diet contained carrageenan, an emulsifying agent that can cause bowel inflammation in animals, and which it has been suggested may have similar effects in humans.¹³ Randomisation was stratified for site of disease between the three categories, small bowel, colonic, and both small and large bowel.

Both diets were given through a fine bore nasogastric tube ('Silk' tube, Corpak Inc, via E Merck Pharmaceuticals, Alton, Hampshire, UK). Each patient received an average of 2250 kcal daily. During the treatment only tap or bottled water was permitted orally. The E028 diet was reconstituted freshly by the patient as required using boiled tap water. All previous treatment including corticosteroids was gradually withdrawn during the first 12 days.

TABLE II Clinical data of patients in both treatment groups before the beginning of the study

	E028	Pepti-2000 LF Liquid
Patients (n)	22	22
Sex M/F	11/11	5/17
Disease location		
Small bowel	7	9
Both small and large bowel	11	10
Large bowel only	4	3
Years since onset of symptoms (mean)	8.6	8.7
Range	0.1–30	0.3–42
Steroid dependent	6	7
Previous surgery		
Right hemicolectomy	7	6
Small bowel resection	2	0
Abdominal mass	1	1
Body weight (% of ideal body weight)	85	88
CDAI mean (range)	285 (164–504)	308 (157–450)

TABLE III Laboratory data of patients in both treatment groups at the beginning of the study. (Mean (SEM))

Normal	E028 (n=22)	Pepti-2000 LF Liquid (n=22)
Haemoglobin		
Male >12.5 g/dl		
Female >11.5 g/dl	11.9 (0.3)	11.6 (0.4)
ESR <20 mm/h	22 (3)	22 (3)
Platelets <400×10 ⁹ /l	439 (26)	487 (32)
CRP <4 mg/l	35 (10)	29 (11)
AAGP <1.2 g/l	1.44 (0.1)	1.56 (0.2)
Albumin >35 g/l	37 (1.1)	36 (1.2)
^{99m} Tc HMPAO scan score (>20=active disease)	96 (16)	98 (24)

Treatment was started in hospital but patients were permitted home once they had stabilised while taking the enteral feed, usually within five days of starting.

Clinical remission was defined as a combination of a reduction in CDAI of 100 points or 40% of the initial value, control of symptoms, and withdrawal of all treatment including corticosteroids. The CDAI criteria for remission was the same as that used in a recent large European trial of dietary treatment.¹⁹

Analysis of the results was performed on an intention to treat basis using Fisher's exact test. The effect of treatment on laboratory and clinical indices was assessed by the paired Student *t* test. The study size was chosen to differentiate between response rates of 75% and 40% at 95% confidence limits.

This study was approved by the ethical committee for the former United Sheffield hospitals. Patients gave informed consent before entry. The patients were entered between August 1989 and January 1993.

Results

Table II compares the treatment groups at the beginning of treatment. They were well matched for previous surgery, time since initial onset of symptoms, corticosteroid dependence, extent of malnutrition, and clinical disease activity. Laboratory indices of activity and ^{99m}Tc-HMPAO scan scores were also similar (Table III).

Table IV shows the overall outcome at the end of 28 days of treatment. Six patients withdrew from the study within the first week because they found nasogastric feeding more inconvenient than anticipated. Sixteen patients achieved clinical remission defined by control of symptoms, withdrawal of all treatment, and a reduction in CDAI of 100 points or 40% from the initial value. Twenty two patients failed to achieve this definition of remission. Of these, 12 patients were withdrawn before 28 days because of failure to show satisfactory

TABLE IV Outcome

	E028	Pepti-2000 LF Liquid
Randomised	22	22
Intolerant of nasogastric feeding	3	3
Failure to achieve remission	11	11
Clinical remission (defined as CDAI reduction of 100 points or 40%)	8	8

Figure 2: Mean changes in CDAI during treatment in patients responding to diet. *Significantly different from initial value, $p < 0.02$.

progress, while 10 improved clinically and completed the 28 days of treatment but did not fulfil the strict definition of remission.

The two diets, E028 and Pepti-2000 LF Liquid had identical rates of remission, failure, early withdrawal, and intolerance of nasogastric feeding. With each diet there were some patients in whom the response was very spectacular, with falls of more than 80% of the initial CDAI value being recorded. Among all the responding patients the rate of improvement was greatest during the initial 10 days of treatment with a slower but sustained improvement in the final 18 days (Fig 2).

In addition to the clinical improvement there was a reduction in CRP in patients achieving clinical remission ($p = 0.05$). In those who started the study with a low serum albumin there was a rise. The other laboratory markers of disease activity (haemoglobin, ESR, platelets, AAGP) and nutritional state (body weight, % ideal body weight) were unchanged by treatment (Table V).

In patients who showed the most spectacular clinical response there was an obvious reduction in inflammatory activity on leucocyte scanning. Figure 3 shows examples of three pairs of scans. Figure 4 plots the results of all the pairs of scans.

The results were analysed to see which particular features of disease were predictive of remission and whether any features precluded a successful response to diet treatment. Some patients of each sex responded rapidly, but in patients intolerant of nasogastric feeding there was a high proportion of men. Analysis by disease location showed that remission was achieved in eight of 16 patients with only small bowel disease, six of 21 with disease at both sites, and two of seven with only colonic disease. Patients with more severe disease, assessed by either CDAI >300 or by a scan score greater than 100, did not show a different rate of response to those with less severe disease. Those with a duration of symptoms of more than five years had a lower remission rate (27%) compared with those with a shorter

TABLE V Laboratory findings at entry and at four weeks in patients responding to diet. (Mean (SEM))

	E028 (n=8)		Pepti-2000 LF (n=8)	
	Day 0	Day 28	Day 0	Day 28
Haemoglobin (g/dl)	12.5 (0.5)	12.3 (0.5)	11.1 (0.6)	11.6 (0.6)
ESR (mm/h)	17 (4)	18 (5)	24 (7)	17 (3)
Platelets ($\times 10^9/l$)	389 (38)	403 (49)	510 (57)	378 (41)
CRP (mg/l)	11 (6)	6 (4)*	48 (23)	0*
AAGP (g/l)	1.2 (0.1)	1.1 (0.2)	1.6 (0.4)	0.9 (0.1)
Albumin (g/l)	39 (1.5)	39 (1.9)	37 (2.2)	40 (1.4)
% ideal body weight	83 (5)	83 (5)	92 (4)	95 (4)

*In combined group of all responders, CRP day 0 v CRP day 28, $p=0.05$. No other change reaches statistical significance (t tests).

Figure 3: Examples of ^{99m}Tc -HMPAO scans before and after diet treatment showing reduction in active inflammation.

history (50%). Previous dependence on corticosteroids did not preclude successful response (three of 13 corticosteroid dependent v 13 of 31 not receiving corticosteroids, reached remission). Patients who had had previous bowel surgery entailing a resection had slightly lower success rates. A low pretreatment serum albumin (below 35 g/l) was also associated with a lower response rate: 29% v 41%. The study size was, however, too small for these subgroup analyses to reach statistical significance.

Four patients who had improved while receiving diet treatment but had not achieved remission required no immediate treatment after completion of the study. Fifteen of the remaining 18 patients, who had failed to achieve remission, were subsequently treated with corticosteroids. One patient opted to try E028, having improved only slightly during the initial 10 days of treatment with Pepti-2000 LF Liquid. She continued to improve and reached remission but is counted as a treatment failure in the above analysis. Four patients had surgery after failing to respond to the diet treatment. Of these one operation was for a perianal abscess, one for obstructive symptoms, and the other two for persistently active inflammatory disease, which had also failed to respond to corticosteroid treatment.

Discussion

This randomised controlled study has confirmed that both a peptide based enteral feed and an amino acid based elemental diet can induce remission in active Crohn's disease. They can be used as the sole treatment, and can be effective regardless of the site or duration of the disease. Some patients who have previously been corticosteroid dependent may also respond to treatment by enteral feeding, permitting withdrawal of oral corticosteroids as reported previously.¹⁰

The amino acid and peptide based diets each achieved the same rate of remission. Some patients in each group had a dramatic response with rapid resolution of symptoms. This rapid response is in keeping with previous reports¹⁴⁻²³ and has also been seen in clinical trials in which amino acid based diets have been compared with corticosteroids.¹⁶⁻¹⁸ The two diets used in our study had similar carbohydrate and fat proportions (Table I), and differed only in their amino acid presentation. E028 being chemically defined contains single amino acids, while Pepti-2000 LF Liquid is derived from hydrolysed whey protein with mean chain length 4.5 amino acids. Because the minimum peptide chain length for antigen presentation is eight amino acids, both diets can be considered to be free of food antigens. From the practical point of view the finding that an oligopeptide based diet seems to be as effective as an amino acid based formula is important, as protein hydrolysates are generally more palatable and can be prepared more cheaply than amino acid based chemically defined diets. At 1992 list prices 28 days of treatment with these diets

Figure 4: ^{99m}Tc -HMPAO scan scores of individual patients before and after diet treatment: E028 v Pepti-2000 LF Liquid. Student's *t* test $p < 0.05$ for each group.

cost £606 for E028 and £340 for Pepti-2000 LF Liquid.

The patients included in this study represent a group of patients who can be difficult to treat. Nearly one third were corticosteroid dependent, half had a CDAI greater than 300, and most had longstanding disease (more than five years of duration). The CDAI can be raised by non-inflammatory complications of Crohn's disease, such as malnutrition, bowel strictures or depression.²⁴ We, therefore, deliberately identified only those patients in whom the inflammatory disease process was active both clinically and on objective laboratory measures of activity. This has permitted us to compare in a controlled trial the ability of these diets to specifically reduce active inflammation.

The trial design included administration of the enteral feed by nasogastric tube in all patients. Both of the diets are moderately unpalatable and although some centres prefer to give them as sip feeds this has an unacceptable intolerance rate of 20 of 51 patients in a recent study.²⁵ Administration by this route also permitted us to be sure that the feed supplied was actually given. In some studies weight loss during treatment must cast doubt on whether this was actually achieved.²⁶

Published works contain reports of diet treatment in retrospective series,^{27 28} non-randomised trials,²⁹ and prospective randomised trials.^{7 11-14 16-19 26} The theoretical ideal of a double blind controlled trial has been performed to compare elemental and polymeric diets but only seven patients were entered into each limb.¹⁴ The retrospective series have reported very high response rates, such as 96 of 113 patients,²⁸ and have shown the need for prospective trials. A formal meta-analysis of the published trials is impossible because the trials differ in patient selection criteria, clinical indices used to follow response, definitions of remission, choice of diets, methods of administration, durations of treatment, and protocols for starting, continuing or withdrawing additional drug treatment. Also some studies cannot be directly compared as they have reported the results in terms of the overall response of the whole group rather than the number of subjects responding.^{7 16-18} Our remission rate is lower than some of the

previous trials, possibly because of the stricter definition of remission and the deliberate choice of patients with active inflammation. All the randomised studies that have reported results as response rates and have used oligopeptide or amino acid based diets, or both, now include 179 patients of which 100 (56%) reached 'remission',^{11-14 19 26} although the definition of remission varies between studies.

There have been no placebo controlled trials of diet treatment in active Crohn's disease. The placebo findings in published reports are of remissions usually achieved after much longer periods. In active disease (CDAI >150) observed for around 100 days the placebo response rate, as defined by CDAI <150 has been reported as 26% in 77 patients in the National Co-operative Crohn's disease study,³⁰ and as 42% in 110 patients in the European Co-operative Crohn's disease study.^{31 32} Historical comparisons would therefore suggest that the achievement of remission with dietary treatment is more effective and substantially quicker than placebo, but probably slower and in some trials less effective than corticosteroids.

All the studies agree that some patients will respond to diet treatment, and that it therefore has a useful role as an alternative where corticosteroids are undesirable, or have failed and surgery is inappropriate. We analysed our results to identify whether any features were associated with a higher remission rate, but found no features that seemed to preclude a response. Patients with recent onset small bowel disease who had not had previous surgery, and in whom the albumin was within the normal range seem to do best.

This is the first clinical trial to prospectively assess dietary treatment by quantitative analysis of scintigraphic images. By this method an objective assessment of the inflammatory activity can be used to provide insight into the mechanism of action of these diets. The scan score fell in 16 of 21 cases reflecting the decreased gut inflammation after treatment. The scan scores did not all fall to within the inactive range, which is consistent with the persistence of histological activity long after a clinical response. The failure to achieve clinical remission in some patients despite substantial falls in objectively measured bowel inflammation highlights the discordance between subjective clinical indices and objective measures of inflammatory activity.²⁴

The mode of action of these diets remains a point of controversy. Several possible mechanisms have been suggested including purely nutritional improvement, bowel rest, changes to the bacterial flora, immune modulation by changes in the fatty acid profile (by arachidonic acid metabolism), direct effect of certain amino acids, such as glutamine, and reduction in the dietary antigen load. In our previous study a whole protein based diet seemed less effective than an amino acid based diet,¹¹ lending some support to the antigen load theory, although subsequently other studies, in some of which malnutrition was

more prominent in the patients before treatment, have found protein containing diets to be effective.^{12-14 33} Even in formula diets containing intact protein, the dietary antigen load is considerably changed, as the protein is usually derived from a single source, usually milk. It may be that further animal models of Crohn's disease will be required before these different theories can be fully tested.³⁴ In this study we have evidence that the oligopeptide and amino acid based diets are exerting a specific anti-inflammatory effect by the reduction in leucocyte migration seen and quantified in the scintigraphic images. Further evidence comes from the reports of decreased protein loss and improvements in abnormal intestinal permeability with diet treatment.³⁻⁵ The concept that luminal contents can in some way modulate activity of inflammation in Crohn's disease is also supported by the finding that diversion of the faecal stream after resective surgery prevents anastomotic recurrence.³⁵ It may therefore be that formula diets reduce or remove some factors responsible for perpetuation of inflammation. Even in cases of small bowel disease the crucial site may be the colonic mucosa,³⁶ although changes in bacterial flora in the colon have been sought and are not seen with elemental diet treatment.³⁷ Immunological analysis of the effects of diet treatment have shown a decrease in HLA-DR antigen expression in the colon and a reduction in gut lavage fluid concentrations of soluble interleukin 2 receptor,^{38 39} but details of the actual therapeutic mechanism remain unclear.

In conclusion, elemental diet is not a panacea in active Crohn's disease. There are patients who respond rapidly and go into complete remission, but there are also patients who derive little or no benefit from it. In those patients who respond there is often an almost total abolition of gut inflammation as shown by scintigraphy in this study. This is further evidence that the effect is more than merely nutritional improvement. We have found an oligopeptide and an amino acid based diet to be equally effective at inducing remission in active Crohn's disease. In some patients either of these types of diet can provide a useful alternative to corticosteroid treatment or surgery.

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