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ORIGINAL ARTICLE

Effects of anti-secretory factor (ASF) on irritable bowel syndrome (IBS)

A double-blind, randomized study

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Abstract

Objective. To evaluate the role of the endogenous protein anti-secretory factor (ASF) on the symptoms, especially loose stools, in irritable bowel ayndrome (IBS). *Design.* A diet with specially processed cereals (SPC) known to induce ASF production was used in patients with IBS, in an eight-week randomized, placebo-controlled study. *Subjects.* Eighty-two patients with IBS were randomized to a diet with either SPC or placebo. *Main outcome measures.* The overall clinical condition and the quality of life were measured by VAS and SF-36 questionnaire, respectively. The plasma levels of ASF were determined in 14 patients with dominating loose stools before and after diet. *Results.* All patients significantly ($p < 0.001$) improved in IBS-related symptoms irrespective of active or placebo diet. In an active-diet sub-group with diarrhoea ($n = 11$) there was a significant ($p < 0.05$) correlation between the increase of plasma ASF level and the improvement on the VAS. *Conclusion.* Both study groups improved significantly on the VAS but no additive effect was seen for the active treatment. In the sub-group with loose stools, the SPC diet induced ASF plasma levels in IBS patients and was correlated to significant symptom improvement in the individual patient.

Key Words: *Anti-secretory factor, diet, family practice, irritable bowel syndrome*

Irritable Bowel Syndrome (IBS) is a common chronic functional disorder, with intestinal dysmotility, as well as secretory and sensitivity disturbances [1]. Recorded prevalence in Sweden was reported to be 12% [2]. The most recent definition of IBS was made in Rome 1999 [3]. No curative treatment has been established and the therapeutic aim is to reduce the symptoms [4]. The condition often severely affects the perceived quality of life, although organic disease is, by definition, absent [5].

The symptoms of IBS are often released by food intake, resulting in many attempts to adjust the composition of the diet [6,7]. A lowered threshold for abdominal discomfort after intake of lipids has been shown by Simren et al. [8], and a changed release of cholecystokinin (CCK) and motilin after a fat meal by Sjölund et al. [9]. Food intolerance in connection with IBS has also been described by some authors [10,11], but not confirmed by others [12]. In several patients there is a visceral hypersensitivity in the gastrointestinal tract for different luminal stimuli inducing exaggerated motility and sensitivity responses [13].

In one-third of IBS patients the symptoms start following gastroenteritis [14,15]. An impaired mucosal barrier may be induced by the gastroenteritis allowing deeper immune response with altered

Specially processed cereals (SPV) induce endogenous production of ASF.

- The increase in IBS patients with loose stools was correlated to the improvement of VAS.
- All IBS patients had a significant improvement on the VAS scale, irrespective of diet.

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sensibility and motor activity to take place [16,17]. It is also possible that persistent low-grade inflammation may be involved in the pathophysiology of IBS [3,18].

Anti-secretory factor (ASF) is a 41 kD protein first described by Lange and Lönnroth in 1984 [19], originally in the rat pituitary, with anti-inflammatory and anti-secretory effects [20]. A diet of specially processed cereals (SPC) stimulated endogenous ASF activity and reduced post-weaning diarrhoea in piglets. Increased levels of plasma ASF were correlated with a positive clinical response [21]. In patients with inflammatory bowel disease (IBD) this diet showed significant improvement of the symptoms [22].

The primary aim in this study was to evaluate whether a diet with SPC could improve the self-assessed general condition in IBS measured on a visual analogue scale (VAS) in a placebo-controlled study during an eight-week period. In a sub-group of IBS patients with dominating diarrhoea, ASF in plasma was measured in order to investigate whether increased levels were associated with clinical response of active diet. This group was selected as analysis of ASF is still based on a biological and very time-consuming method.

Material and methods

Patients and study procedure

Eighty-two persons (80 originally planned, two replacing patients with insufficiently completed diaries) from southern Sweden (55 females, 27 males) with a median age of 44 years (range 18–74 years) and with a median BMI of 25 kg/m^2 (range 19–36 kg/m^2) were recruited to the study at the Health Care Centre of Dalby or from nearby healthcare centres. Contacts with the patients were taken mainly after a search for the diagnosis from our own medical records and after referral from other units. Occasional patients were referred on a personal basis. The inclusion criterion was an established diagnosis of IBS, based on the Rome criteria for IBS. The patients should have a history for at least two years or a normal barium enema of colon during the last six months, when the history did not exceed two years. In 42 of 82 patients barium enema colon examination had been performed and in 12 a colonoscopy. Eleven had had both examinations done.

The degree of discomfort related to the IBS was recorded on a VAS (range 0–100 mm). In order to ensure a minimal level of discomfort of the IBS condition, registration of a minimum of 40 mm was the limit to make the patient eligible for inclusion in the study. Five patients registered lower discomfort than this limit and six patients referred to the study were not included due to dominant constipation. At the screening visit a standard clinical examination was performed in order to exclude the usual gastrointestinal diseases of importance. Blood samples were collected for haemoglobin, glucose, liver enzymes, creatinine, C-reactive protein (CRP), orosomucoid and ASF level in plasma before the start of the study and after eight weeks' treatment.

The mean duration of the IBS condition was 14 years (range 19 months to 58 years). Data were recorded concerning the intensity of the different symptoms, such as abdominal pain, flatulence, frequency and consistency of stools.

The study was approved by the ethical committee of the University of Lund and the patients took part after giving informed consent.

The diet

The cereals of the active food were treated hydrothermally in a process according to the procedure described by Björk et al. [22].

Both active and placebo food had the same energy and nutrient content. The food consisted of muesli, cracker, or a biscuit, produced by BioDoc AB (Box 30192, S-104 25 Stockholm, Sweden). The food in the two different groups was equal in taste and appearance. A panel had previously ensured no detectable difference in active or placebo food treatment [21]. Randomization was made in blocks of four in proportion 1:1 for active versus placebo.

The diet was introduced after a two-week run-in period and used for eight weeks. The patient was requested to take three units per day. One unit was defined as a biscuit, a cracker, or 100 g of muesli. The normal diet was intended to remain unchanged. After four weeks another visit was made to ensure the correct use of the diet. After a further four weeks of diet, the study was ended by two weeks' post-treatment registration.

Analyses of ASF

Plasma ASF was analysed by a biological method according to the procedure described by Björk et al. [22] at the Department of Medical Microbiology, Sahlgrenska University Hospital, Gothenburg. ASF was measured in arbitrary units (AU). Inhibition of the intestinal secretion in a rat was compared with that of a known standard concentration. A reduction of the secretion by 50% corresponds to a level of 1.0 AU. Our collected samples were stored at -38°C for six to 24 months until analysis.

Diary

In the two-week period prior to treatment and during the last two weeks of the eight-week treatment period the patient filled in a diary concerning abdominal pain, presence of bloating and flatulence, consistence of faeces, and frequency of bowel movements. The consistency of the faeces was given in three grades: loose, normal, or hard. The patients filled in the SF-36 questionnaire [23] measuring quality of life before the start and after the treatment period.

Statistical methods

The differences between the groups on the VAS were analysed by Student's t-test as well as a Wilcoxon two-sample test. For the assessment of effects on the psychological and mental components of the SF-36 the Wilcoxon two-sample rank-sum test was used. The correlation between the change from baseline to follow-up in plasma ASF values and the change in the value on VAS was assessed by Spearman's test. A p-value of less than 0.05 was considered significant.

Results

Diary and diet

Eighty out of 82 patients completed the diary during the run-in period. Those with 10 or more recorded days during this two-week period were considered evaluable (n = 80, two had recorded less than 10 days). Sixty-seven patients performed the whole diet period, and returned for the final visit. Sixty-one of these were compliant with the intake of food, the cut-off for compliance being experimental food taken for at least 75% of the days (Figure 1). The rate of discontinuation was 15/82 patients equalling 18%.

The average number of bowel movements before treatment was 1.7 per day (range 0.4–7.1) and after eight weeks it was 1.6 per day (range 0.6–5.8). Forty patients had decreased stool frequency and 26 increased frequency, equally distributed between the active and placebo group, i.e. 20 and 13 respectively. The sub-group as a whole with severe diarrhoea (level 3 out of 3, self-assessed) at baseline had no change in their bowel habits.

VAS symptoms

Although there was a major improvement in the overall VAS for the symptoms from baseline to end of treatment in both the active and placebo group ($p < 0.001$), there was no significant difference in VAS between the two experimental groups based on active versus placebo treatment. The statistical evaluation of VAS is based on the inter-individual difference from baseline. Analysis was also made for sub-groups according to sex, age, weight, BMI, time of year entering study, time since diagnosis, degree of abdominal pain, consistency of stools, and food variation, with no significant influences on VAS or in the quality of life questionnaire.

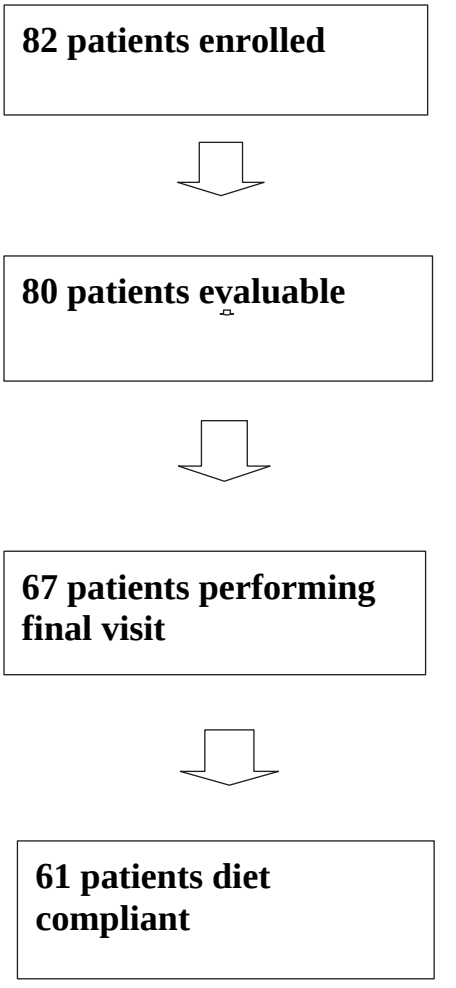

Figure 1. Flow chart for patients.

Plasma ASF levels and their correlation with VAS

ASF was analysed in plasma for 14 patients with the most severe condition, equalling three out of three on a self-assessed scale, of loose stools. Since the randomization procedure did not take this parameter into consideration the two groups turned out to be unequal with 11 patients on active treatment. Of these, eight of 11 increased their ASF levels, two to a level above 1.0 AU and six more to a level above 0.4 AU. Of the placebo patients one showed a slight increase and one a decrease in ASF levels. The two patients with the largest increase also had a large improvement in their clinical symptoms. A strong

statistical correlation was found between change in VAS and change in ASF ($p < 0.0001$, covariance analysis).

Laboratory tests

For the laboratory tests, except for ASF, there was no significant change between baseline values and the tests done after eight weeks treatment.

Quality of life questionnaire

The SF-36 (quality of life) questionnaire can be divided into different sub-groups, i.e. physical and mental components. Taken separately there was a significant ($p = 0.02$) difference in MCS variable whereas there was none in the PCS between the active and the placebo group (Table I).

Discussion

Our study with special diet treatment in IBS patients is, to the best of our knowledge, one of the largest placebo-controlled IBS intervention studies in primary healthcare. The eight-week period is as long as could be seen as reasonable concerning interpretation of the results. The dropout rate of 18% is also significantly low. The outcome of the self-recorded measurement of overall clinical condition and symptoms on the VAS showed a significant improvement in all patients, and no significant difference between special diet and placebo. This may be explained by either of two proposed effects in IBD: an anti-inflammatory and an anti-secretory one. However, both diets most probably had a bulking effect with possible benefit in the two IBS groups irrespective of the ASF levels. Also, it is well known that patients with this condition tend to benefit in symptoms by taking care and medical visits.

Few studies, except for studies including a fibre-rich diet, have been published concerning the efficacy of diet in IBS. The number of randomized controlled trials with bulking agents is low [24,25]. In two studies with ispaghula [26] and bran fibre [27] a significant improvement was seen. In another study there was no such observed difference [28].

The contribution of the special diet may therefore be too small to be detectable, especially as this group of patients shows a high placebo response [29,30]. The IBS group of patients is very heterogeneous and thus bowel function might be improved in sub-groups with this treatment. Since the method of analysing ASF is complicated and the laboratory resources at this particular time were limited, we had to limit the analyses to the patient group with the most severe loose stools ($n = 14$). However, the symptoms in these latter subjects did not differ between patients on active diet compared with those on placebo diet. The relative disproportion between active diet and placebo, 11 to three, in this group is merely a result of chance. To judge if the active diet really was able to induce increased ASF levels, plasma ASF was measured in these patients. Here we also found a significant correlation ($p < 0.05$) between the increase in plasma ASF and the improvement on VAS, by use of the active diet in the individual patients. Because a rank variable was used as the dependent variable when analysing the correlation between change in VAS and change in ASF the beta coefficient cannot be given a meaningful interpretation, which is why it is not provided. Thus, this kind of treatment, with its potential anti-secretory properties, may be best suited for the sub-group with dominating loose stools. This conclusion should be confirmed in larger studies.

In conclusion, our placebo-controlled diet study in IBS patients showed an overall improvement in symptoms irrespective of diet. No additive effect of the ASF-inducing diet was seen. This may be due to a too small a study group as these patients have a high placebo response. However, for the sub-group with the most prominent diarrhoea symptoms there was a positive correlation between the induction of ASF and improvement in symptoms individually.

Table I. Demographic data on patients including p-values for the differences between the groups.

	Active treatment	Placebo	p-value
Mean age (years)	42.2	44.4	n.s.
Female (%)	67	68	n.s.
SF-36 (PCS)	44.7	45.5	n.s.
SF-36 (MCS)	37.2	43.3	0.02
VAS median, visit 2	72	70.4	n.s.
IBS duration mean (years)	13.8	13.7	n.s.
Initial diary results			
No reliable days	13.3	13.4	n.s.
No bowel movement	22.6	24.7	n.s.
No loose stools	5.2	9.3	0.01
No hard stools	4.4	4.8	n.s.
Lab parameters			
Hb (g/l)	134.6	136.6	
SR (mm)	8.5	8.6	
CRP	6.3	5.8	
ASAT	0.43	0.43	
ALAT	0.43	0.34	
ALP	2.45	2.65	
Creatinin	67.3	69.8	
Orosomucoid	0.75	0.73	

Notes: PCS = physical component scale; MCS = mental component scale; p-values for lab parameters were not calculated.

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