

Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel syndrome due to food intolerance

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Summary

Twenty patients with irritable bowel syndrome due to food intolerance were randomized to either oral sodium cromoglycate or placebo in a double-blind cross-over trial. The study consisted of treatment with either sodium cromoglycate or placebo for 8 weeks, followed by the cross-over treatment for 8 further weeks. Patients were allowed to eat the offending foods during the study. Eighteen patients completed the study. Analysis of patients' diary card scores showed a statistically significant difference in favour of sodium cromoglycate. There was a long carry-over effect in the active-placebo order group. Therefore oral sodium cromoglycate seems to be a useful treatment in patients with irritable bowel syndrome and proven food intolerance.

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Introduction

The irritable bowel syndrome (IBS) is a chronic disease of the gastrointestinal tract characterized by abdominal pain, distention and either diarrhoea or constipation [1] without radiological or histological evidence of organic disease. It accounts for up to 50% of the referrals to gastroenterology clinics [2] but its pathogenesis is poorly understood [3]. The cause of IBS remains unknown; it has been suggested that the aetiology is psychosomatic.

Treatment is usually unsatisfactory and consists of antispasmodics, bulking agents and tranquillizers. Psychotherapy and hypnotherapy have been reported to be highly effective [4–6].

The role of diet remains controversial [7,8]; however, food intolerance may be a factor involved in the pathogenesis of IBS. Many investigators [9, 15] have shown by double-blind challenges that individual foods can trigger symptoms in some patients; nevertheless, the percentage of patients that benefit from dietary manipulation ranges from 15% to 67% in different reports [11,15].

Orally administered sodium cromoglycate appears to decrease gastrointestinal permeability [16–19] and has been shown to be useful in preventing symptoms due to adverse reactions to food [20–22] and dietary additives [23]. Unfortunately, these findings could not be reproduced in other studies [24,25]. The aim of this study was to determine whether oral sodium cromoglycate has beneficial effects in patients with IBS due to food intolerance.

Patients and methods

Patients

Twenty patients (18 women, two men; mean age 33.5 years) with diagnosis of IBS due to food intolerance were entered into the trial after giving informed consent. The diagnosis of IBS was established on the basis of the clinical history (episodic abdominal pain, distension and diarrhoea lasting for at least 1 year), a normal clinical examination, a normal barium enema, negative stool cultures, a normal full blood count, erythrocyte sedimentation rate, serum biochemical profile and serum thyroid hormones (T_3 , T_4 and FT_4). Five patients underwent colonoscopy and had mucosal biopsies. In all the patients conventional therapy had failed to induce a symptomatic response.

The diagnosis of food intolerance was based on the

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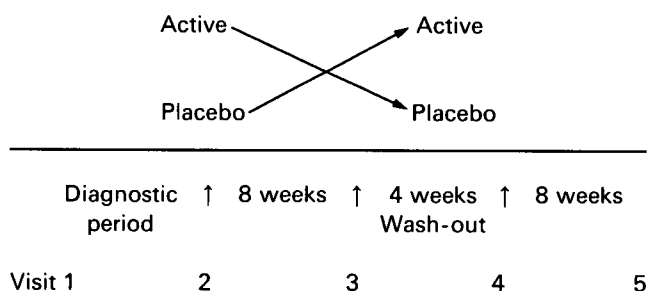


Fig. 1. Protocol for double-blind cross-over study of oral sodium cromoglycate given to patients with irritable bowel syndrome due to food intolerance.

remission of symptoms following 3 weeks of an elimination diet and relapse of symptoms after both an open and double-blind challenge tests. Only two patients had true food allergy with a positive and concordant skin-prick test, challenge test and serum-specific IgE. Most of the patients (11 subjects) were intolerant to wheat; the others were intolerant to milk (six patients), to fruit and vegetables (six patients) and to egg (three patients). Some subjects were intolerant to more than one food.

The patients intolerant to wheat were shown not to have coeliac disease, either by a normal jejunal biopsy (seven subjects) or by the absence of serum IgA anti-gladiadin antibodies (four subjects). Lactose tolerant tests were performed to exclude lactase deficiency.

Methods

The trial design was an 8 × 8-week double-blind cross-over study, during which the patients were allowed to consume the incriminated food.

Figure 1 shows a summary of the trial design.

Ten patients received oral treatment in the order placebo–active and 10 patients received the treatment in the order active–placebo; one patient from each group had to be withdrawn because of complications.

The two treatments were separated by a 4-week wash-out period.

The active treatment consisted of 2000 mg/day of sodium cromoglycate, divided into four equal doses, 30 min before each main meal and at night. The capsules had to be opened and the powder dissolved in warm water before swallowing. No other treatments were allowed during the study.

During the trial patients recorded the severity of each symptom on a daily card, using a scale from 0 to 2 in which 0 = none; 1 = moderate; and 2 = severe. Thus the maximum daily score for all symptoms was 6.

Table 1. Mean value of symptom scores in the placebo–active order group

Treatment period (weeks)		Mean score ± s.d.	P*
Placebo	0	4.12 ± 1.32	—
	2	3.39 ± 2.09	0.02
	4	3.50 ± 2.05	NS
	6	3.57 ± 1.86	NS
Wash-out	8	3.65 ± 1.82	NS
	2	3.67 ± 1.75	NS
	4	3.76 ± 1.80	NS
	6	3.76 ± 1.80	NS
Active	2	2.65 ± 2.02	0.03
	4	2.63 ± 1.91	0.04
	6	2.32 ± 1.74	0.03
	8	2.26 ± 1.92	NS

* The analysis is referred to the starting value. NS, not significant.

Statistical analysis

The Wilcoxon signed ranks test was used to analyse the data.

Results

Eighteen of the twenty patients completed the study. There was no statistically significant difference between the two groups when the starting values of the symptoms were compared ($P=0.6$).

Two patients did not experience any improvement, and one patient improved following placebo but not active treatment.

Table 1 shows the results in the placebo–active arm of the study. After 2 weeks of placebo, there was a small but statistically significant improvement ($P=0.02$) which is not observed in the following 6 week period on placebo. A beneficial effect on active treatment was seen during the first 6 weeks ($P=0.03$).

This beneficial effect did not reach statistical significance during the last 2 weeks; however, during this period one patient had severe diarrhoea and abdominal pain which improved immediately after the withdrawal of sodium cromoglycate. Further analysis of benefit on active treatment, with this patient excluded, showed $P=0.03$.

Table 2 shows the data from the active–placebo arm of the trial. In this group the statistically significant improvement present during the active treatment period remained until the week 6 of the placebo treatment period.

Table 2. Mean value of symptom scores in the active-placebo order group

Treatment period (weeks)		Mean score $\pm$ S.D.	P*
Active	0	3.79 $\pm$ 1.67	—
	2	2.17 $\pm$ 1.38	0.005
	4	2.14 $\pm$ 1.43	0.005
	6	2.04 $\pm$ 1.32	0.009
	8	1.59 $\pm$ 1.42	0.006
Wash-out	2	2.56 $\pm$ 1.71	0.01
	4	2.74 $\pm$ 2.05	0.02
Placebo	2	2.91 $\pm$ 1.83	0.05
	4	2.36 $\pm$ 1.86	0.009
	6	2.73 $\pm$ 1.53	0.02
	8	3.10 $\pm$ 1.68	NS

* The analysis is referred to the starting value. NS, not significant.

Table 3. Mean value of symptom score (considering all the patients)

Starting value	After placebo treatment	After active treatment	P
3.94 $\pm$ 1.49	3.34 $\pm$ 1.71		0.2*
3.94 $\pm$ 1.49		1.89 $\pm$ 1.65	0.001
	3.35 $\pm$ 1.71	1.89 $\pm$ 1.65	0.003

* Not significant.

If both arms of the trial are combined, sodium cromoglycate is significantly ($P < 0.003$) superior to placebo (Table 3).

Discussion

The clinical management of patients who have adverse reactions to food is avoidance of that individual food. The maintenance of a restricted diet becomes very difficult when patients are intolerant to a common foodstuff (such as cereals in Italy) or to a large number of foods. In such cases, a therapeutic approach becomes necessary.

Here we evaluated the effects of oral sodium cromoglycate in 18 patients with IBS due to food intolerance. Only in two patients was it possible to establish an IgE mediated mechanism. As in other studies [10,19] we also found that in the majority of these patients there was no evidence of an immunological cause for the food intolerance.

Buisseret *et al.* [26] have demonstrated that rises of

PGE₂ and PGF₂ levels correlate with the food challenge and abdominal symptoms; administration of prostaglandin synthetase inhibitors reduced the rise in circulating and stool prostaglandin levels, and improved abdominal symptoms [27].

The detection of circulating immune complexes, measurement of raised serum levels of food antigens and the assessment of intestinal absorption have failed to distinguish between those patients with IBS who will improve on a diet and those whose symptoms will remain unchanged [19].

The usefulness of oral sodium cromoglycate in adverse reactions to food is still highly controversial [20,24]; moreover, while some investigators report its beneficial effect only in patients with true food allergy [21], others have shown its effectiveness also in food-additive intolerance [23]. Oral sodium cromoglycate has the ability to inhibit the release of mediators from mast cells and other inflammatory cells; it has been reported to be capable of inhibiting the passage of macromolecules across the intestinal mucosa [17,18], thus preventing the formation of circulating immune complexes [28].

In our study two patients out of 18 did not improve during the whole treatment, and one patient improved on placebo treatment. It is worthwhile to notice that in the placebo-active order group there was a statistically significant improvement after 2 weeks of treatment, demonstrating the placebo effect. This effect disappeared during the following weeks. One patient had severe diarrhoea during the last 2 weeks of active treatment, but improved immediately after the drug withdrawal. It is unusual for such a side effect to manifest itself so late in treatment.

In the active-placebo order group, the benefit continued during the wash-out period and most of the placebo treatment periods. This is almost certainly due to a carry-over effect of sodium cromoglycate. Other investigators [29] have also observed a similar carry-over effect with oral sodium cromoglycate.

It is likely that after a long period of treatment, patients would be protected by taking the drug only before eating the offending foods.

We have demonstrated that oral sodium cromoglycate is a useful treatment in patients with IBS due to food intolerance. The conflicting results obtained by earlier studies may be explained by the lower dosage and shorter treatment periods used, compared with our study. In addition, our patients were carefully selected and had specific food intolerance proven by an elimination diet and a double-blind challenge test. We allowed the patients to eat the incriminated foods during the trial, in order to evaluate the protective effect of the drug on a normal diet.

Despite a response rate of 15 out of 18, we would not advocate oral sodium cromoglycate as a diagnostic aid in patients with IBS; first, because the incidence of food intolerance in subjects with IBS is unknown, and second, because we think that elimination diet is still the most reliable and the least expensive diagnostic procedure when food intolerance is suspected.

We therefore conclude that in patients with IBS and proven food intolerance a long treatment period with a high dose of oral sodium cromoglycate may be useful.

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