

Oral Sodium Cromoglycate Treatment of Atopic Dermatitis Related to Food Allergy

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Thirty-two children and two adults with chronic atopic dermatitis related to food allergy entered this double-blind crossover study comparing oral sodium cromoglycate (200-1600 mg/24 h) with placebo. Each treatment period comprised 6 weeks: 4 weeks on elimination diet, and 2 weeks on a normal, i.e. unrestricted diet. The diagnosis of food allergy was made after clinical improvement with elimination diet and relapse after challenge. Overall analysis of skin symptoms evaluated by means of clinical assessments and diary cards, opinions of treatment, and use of concomitant medication gave no evidence of any difference between sodium cromoglycate and placebo. Unusual symptoms were reported by 18 patients. In one case the patient was withdrawn during the sodium cromoglycate period because of side effects. The majority of symptoms with both treatments were stomach problems. Overall analysis of the laboratory data gave no significant differences between treatments.

Keywords: atopic dermatitis; double-blind crossover trial; food allergy; sodium cromoglycate.

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Oral sodium cromoglycate has been reported to be effective in the prevention of various conditions caused by food allergy or intolerance (9, 10, 11, 16, 19). In open studies (8, 18) oral sodium cromoglycate was found effective in the treatment of atopic dermatitis related to food allergy. Businco et al. (7) confirmed this in a controlled trial. Others (1, 17) have not been able to reproduce these results in controlled trials.

Attempts to treat atopic dermatitis with ointments containing sodium cromoglycate have also been undertaken. Haider (12) reported that topical sodium cromoglycate was effective, while Zachariae et al. (21) were unable to confirm this.

This study deals with a placebo controlled double-blind crossover trial of oral sodium cromoglycate in patients suffering from atopic dermatitis related to food allergy.

MATERIAL AND METHODS

Patients

Thirty-four patients, admitted to the Children's Allergy Clinic, Rigshospital, Copenhagen, with clinically typical atopic dermatitis of varying severity took part in this trial. Sixteen patients had a mild, another 16 a moderate and two a severe degree of atopic dermatitis. Informed consent was obtained from all the patients or their parents. Some patient characteristics are shown in Table 1.

All patients had experienced improvement in their eczema when on elimination diet, and relapse after including the causative foods at least twice, and the majority were challenged three times. Eighteen patients were challenged within 3 months of their participation in the study, 16 within the last year. Some of these

had experienced exacerbation of their eczema within this year when breaking the diet. The foods which most often caused symptoms were eggs, milk, fish, various fruits/vegetables, and nuts. In 18 patients foods caused associated symptoms such as asthma, rhinitis, urticaria, vomiting and/or diarrhoea. Twenty-nine patients had at least one positive skin prick test reaction (a wheal = that produced by histamine chloride 1 mg/ml, at least 3 mm) to a food. Two patients had no positive skin prick tests, and in three patients skin tests were not performed. Twenty-eight patients used topical steroids, one used tar ointment, and 13 antihistamines. None used oral steroids. Before entering the trial all but one avoided one or more causative foods. Twelve patients used concomitant asthma medication (β_2 -agonists and/or theophylline), two used sodium cromoglycate Spinhaler[®], and one beclomethasone spray.

Experimental design

The study was designed as a double-blind cross over trial with a 2-week baseline, 6 weeks in each treatment period and a 2-week follow-up after each treatment period. During the whole trial, except for the last 2 weeks in each treatment period, the patients followed their individual elimination diet, excluding the foods suspected of aggravating the eczema. During the last 2 weeks the causative foods were gradually introduced into the diet over 3 days. The patients or parents were asked to record the introduced foods for the first 3 days in order to

be able to introduce foods in the same amounts and order in the second period. Patients who did not develop symptoms, or only few symptoms, went on to an unrestricted diet for the remainder of the treatment period, and the foods were no longer recorded. Patients who developed heavy symptoms returned to the elimination diet.

Each patient visited the clinic 10 times: before and after the baseline period, after 1, 4, and 6 weeks of each treatment, and just after the end of each follow-up period. In addition, a telephone consultation could be made after 2 weeks of each treatment to confirm the final dose of test treatment. At each visit the severity of eczema was assessed by means of an area score chart. For each of 20 areas of the body the severity of redness, vesiculation, weeping and crusting, excoriations, and lichenification was recorded on a scale of 0 to 10. These scores were used to give a mean score for the whole body, both for individual symptoms and overall. In addition, an assessment of the general severity of eczema was made using the same symptoms and scale. For area scores and general severity, comparisons were made after 1, 4, and 6 weeks of treatment. Furthermore, a comparison was made using the difference in scores between 6 weeks of treatment and 4 weeks of treatment (food challenge - elimination diet).

At each visit the use of local steroids was calculated by weighing the tube. The opinions of the patients, parents, and clinician concerning the treatment and unusual symptoms were recorded after 1, 4, and 6 weeks of treatment.

Table 1
Patient characteristics

Treatment order	Male	Female	Age mean (range)	Age at onset (months) mean (range)	Family history of atopy	Other atopic diseases	Serum IgE, baseline mean (range)
S-P	7	10	5.9 (1-18)	6.9 (< 1-24)	14	17	1966 (< 10-17000)
P-S	10	7	6.9 (2-23)	13.4 (< 1-84)	16 (1 adopted)	14	1501 (10-19475)

S-P = Sodium cromoglycate-Placebo group; P-S = Placebo-Sodium cromoglycate group, IgE (Phadebas[®] PRIST).

Laboratory tests were made at the end of baseline and at the end of each treatment period (Table 2).

Almost all patients were evaluated by one of the authors (P.D.).

Diary cards for self-assessment of itch, sleep difficulty, eczema, use of concomitant medication, and probable side effects were kept throughout the trial. Each symptom was recorded on a scale of 0 to 10. For each symptom the means were calculated for each 2 weeks of each treatment period.

Medication

The active treatment was sodium cromoglycate 2% or 4% (depending on weight) with a matching placebo given in four divided doses. The patients were asked to take the drug 15 min before meals and at bedtime. The final dose was from 20 to 40 mg/kg/24 h, up to a dose of 1600 mg/24 h.

Table 2
Laboratory tests

Haemoglobin, leucocytes, differential count, serum sodium, potassium, bilirubin, GOT, alkaline phosphatases, creatinine, eosinophils, IgE, urine protein, glucose, blood, blood pressure
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Statistics

For individual order groups (i.e. sodium cromoglycate/placebo or placebo/sodium cromoglycate) treatments were compared using a Wilcoxon Matched-Pairs Signed-Ranks Test. A comparison of treatments for all patients was made by performing a Mann-Whitney U-test on the differences in scores for the first and second treatment periods. The latter was used, because there was strong evidence that period effects were present for the symptoms "itch" and "eczema" on the diary cards (15). For clinical assessments, medication, and laboratory data no period effects were present.

RESULTS

In the sodium cromoglycate/placebo group two patients withdrew during the first treatment period. In one case because the mother felt that her son was better and refused the second treatment. The other patient withdrew because of stomach-ache, nausea and headache.

Diary scores

Strong evidence of period effects for severity of "itch" and "eczema" in weeks 1-2 and 3-4 of treatment was detected, the mean being higher in the second treatment period for both the

Table 3

Diary card symptom scores. Mean scores from weeks 3-4, weeks 5-6 and weeks 6-1 (i.e. food challenge - elimination diet) of active treatment compared with mean scores from corresponding weeks of placebo treatment

Treatment order	Weeks	Sample size	Itch			Sleep difficulty				General severity of eczema			
			Mean			Mean				Mean			
			SCG	P	Significance	Sample size	SCG	P	Significance	Sample size	SCG	P	Significance
S-P	3-4	15	2.89	3.19	NS	15	1.15	0.99	*	15	3.39	3.80	NS
P-S	3-4	17	3.80	3.22	**	16	0.62	0.54	NS	17	4.08	3.24	**
S-P	5-6	15	3.60	3.87	NS	15	1.55	1.35	NS	15	4.45	4.15	NS
P-S	5-6	17	3.64	3.43	NS	17	0.67	0.49	NS	17	3.95	3.52	NS
S-P	6-4	15	0.71	0.68	NS	15	0.39	0.36	NS	15	1.06	0.35	NS
P-S	6-4	17	-0.16	0.21	NS	16	-0.15	-0.22	NS	17	-0.13	0.28	NS

SCG = Sodium cromoglycate; P = Placebo; S-P = Sodium cromoglycate-Placebo group; P-S = Placebo-Sodium cromoglycate group; NS = Not significant ($P > 0.05$); * = $P < 0.05$ in favour of placebo; ** = $P < 0.01$ in favour of placebo.

sodium cromoglycate/placebo and the placebo/sodium cromoglycate groups. Overall there were no significant treatment effects. For individual order groups there were several significant differences between treatments (Table 3). This would be expected, as there was a significant period effect.

The results of the analysis for weeks 1–2 are omitted, as they were similar to those shown in the tables.

It should be mentioned that there was only little exacerbation of symptoms during the challenge periods.

Clinical assessments

The analysis for general severity is shown in Tables 4a and b. There were three significant differences between treatments, all in the sodium cromoglycate/placebo group. In each case the difference was in favour of placebo. Overall there were no significant differences between treatments.

Many of the differences in scores between food challenge (week 6 of treatment) and elimination diet (week 4 of treatment) were slightly negative, indicating possible improvement after food challenge.

Use of concomitant medication

Because patients frequently forgot tubes or changed to new tubes between visits, use of steroids could only be calculated for 10 patients in the sodium cromoglycate/placebo group and for nine in the placebo/sodium cromoglycate group (5 last weeks of each treatment period). Six patients in the sodium cromoglycate/placebo group and seven in the placebo/sodium cromoglycate group used antihistamines. For neither steroids nor antihistamines were there any significant differences between the groups.

However, on the average, the patients in both groups used 50–60% more steroid ointment per week during the provocation period than during the preceding treatment period (Table 5).

Patients, parents and clinicians had no preferences for either treatment (Table 6).

Eighteen patients reported unusual symptoms (Table 7). Only one patient had to withdraw because of side effects.

Laboratory data

There were no consistent changes in peripheral blood eosinophil counts or IgE measurements

Table 4a

Clinical assessments of general severity of eczema. Mean scores from weeks 3–4, weeks 5–6 and weeks 6–4 (i.e. food challenge – elimination diet) of active treatment compared with mean scores from corresponding weeks of placebo treatment

Treatment order	Weeks	Redness				Vesiculation, weeping, and crusting				Excoriation				Lichenification			
		Mean			Significance	Mean			Significance	Mean			Significance	Mean			Significance
		Sample size	SCG	P		Sample size	SCG	P		Sample size	SCG	P		Sample size	SCG	P	
S-P	3–4	15	4.40	4.40	NS	15	4.20	4.47	NS	15	3.27	3.53	NS	15	3.27	3.80	NS
P-S	3–4	16	3.41	3.50	NS	16	3.56	3.19	NS	16	2.63	2.41	NS	16	2.91	2.44	NS
S-P	5–6	15	3.93	3.80	NS	15	4.13	4.07	NS	15	3.93	2.47	*	15	3.87	3.20	NS
P-S	5–6	16	3.00	3.44	NS	16	3.50	3.69	NS	16	2.38	2.56	NS	16	2.56	2.94	NS
S-P	6–4	15	-0.47	-0.60	NS	15	-0.07	-0.40	NS	15	0.67	-1.07	*	15	0.60	-0.60	*
P-S	6–4	15	-0.47	-0.33	NS	15	-0.20	0.13	NS	15	-0.40	-0.20	NS	15	-0.47	0.27	NS

in the individuals, and no significant differences between the groups could be detected. Protein, blood or glucose were found in seven urine tests in six children, two at the end of baseline period and five after treatment with sodium cromoglycate. The findings could not be reproduced. Blood pressure was within normal limits in all patients.

DISCUSSION

Several studies indicate that allergic mechanisms play a role in the pathogenesis of atopic dermatitis (2, 4, 14). As oral sodium cromo-

glycate is only absorbed to a very small extent (20), its possible effect is assumed to take place in the gut. Jackson et al. (13) have shown that the permeability of the gut is increased in patients with atopic dermatitis. Brostoff et al. (6) found large amounts of circulating immune complexes containing IgE in food-allergic patients with symptoms from various organ systems, but pretreatment with oral sodium cromoglycate greatly diminished the amount of immune complexes and abolished symptoms.

More recently Brostoff & Carini (5) reported similar results, and found circulating immune complexes containing IgG and IgE, as well as free antigen, in serum from food-allergic patients after challenge. The production of both IgG and IgE complexes was prevented, and the level of food antigen reduced, by oral sodium

Table 4b

Clinical assessment of general severity of eczema.

Mean scores from weeks 3-4, weeks 5-6 and weeks 6-4 (i.e. food challenge - elimination diet) of active treatment compared with mean scores from corresponding weeks of placebo treatment

Overall					
Mean					
Treatment order	Weeks	Sample size	SCG	P	Significance
S-P	3-4	15	3.78	4.05	NS
P-S	3-4	16	3.13	2.88	NS
S-P	5-6	15	3.97	3.38	NS
P-S	5-6	16	2.86	3.16	NS
S-P	6-4	15	0.18	-0.67	NS
P-S	6-4	15	-0.38	-0.03	NS

Abbreviations see Table 3.

Table 5

Use of steroid ointment (g)

		Elimination diet (3 weeks)		Challenge (2 weeks)	
Sample size	Treatment order	SCG	Placebo	SCG	Placebo
10	S-P	4.6	4.0	6.3	4.9
9	P-S	6.9	6.2	6.2	5.5
19	Total	11.5	10.2	12.5	10.4

Table 6

Patient's or parent's and clinician's opinion of treatment

General severity of eczema	Patient/parent		Clinician	
	SCG	Placebo	SCG	Placebo
Very much better	0	3	0	0
Somewhat better	7	8	11	13
No change	11	11	11	12
Somewhat worse	11	10	10	7
Very much worse	3	0	0	0

Table 7

Unusual symptoms during treatment with:	SCG	Placebo
Nausea and vomiting	4	1
Stomach-ache	5	4
Diarrhoea	4	2
Thin/smelly/frequent faeces	3	5
Eczema/itching	2	1
Infections/fevers	6	2
Headache	1	1
Thirst	1	0
Enormous appetite	1	0
Pale and car sick	1	0
Appendicitis	1	0
Bad breath	0	1
Asthma worse	0	1

cromoglycate. Furthermore, no symptoms occurred. Thus the action of sodium cromoglycate is thought to be a blocking of the IgE-mast cell reaction in the gut preventing the local inflammatory allergic reaction. This would lead to diminished food antigen absorption, preventing or diminishing the production of immune complexes and therefore preventing symptoms.

However, our study failed to confirm the efficacy of oral sodium cromoglycate in patients with atopic dermatitis related to food allergy, as did Atherton et al. (1). They suggested that the failure of sodium cromoglycate might be ascribed to too small doses, or that the drug was given at the wrong times. Apparently they used the same dose, 400 mg/24 h for all patients (children aged 2–10 years), corresponding to doses from 12 to 35 mg/kg/24 h. However, they had found larger doses ineffective in a previous pilot study (1).

We used doses of 20–40 mg/kg/24 h given in four divided doses, and the patients were asked to take the drug before meals and at bedtime. However, this was not possible for all patients. One third spent some time of the day in kindergartens, and some of these refused to give the children drugs. Thus, five children did not have the drug at noon, 5 days a week, but in mid-afternoon when they returned home.

Atherton et al. (1) also speculated that airborne antigens may be important in children with atopic dermatitis. Therefore, sodium cromoglycate might have been effective if the drug had been administered by the nasal, oral and bronchial route concurrently. Our study was performed during autumn, winter and spring, when the number of airborne antigens is less.

In our study there was, on average, only little if any exacerbation of skin symptoms after food challenge according to diary scores and clinical assessments. However, the symptoms may have been masked by the use of more steroid ointment during the provocation period, but no significant difference in the use of steroids was found, whether the patients were on active or placebo treatment. Unfortunately, the exact amount of steroids used could only be calculated for 19 patients.

Furthermore, two patients had to return to their diet after 1 or 2 days, because challenge caused heavy symptoms. Thus their eczema had improved when they were seen at the clinic 12 or 13 days later. Thirdly, some patients may not have eaten allergenic foods every day, as they were supposed to. This was not specifically asked for in the diary cards. Lastly, it could be argued that some patients were not allergic to the suspected foods. On the other hand, the patients had been challenged at least twice before entering the study, and concomitant medication increased during the provocation period.

In a controlled trial of patients with atopic dermatitis Lindskov & Knudsen (17) reported significant differences in favour of oral sodium cromoglycate compared to placebo in the investigators' assessments of eczema after 6 weeks' treatment. However, no differences were found in the investigators' assessment of lichenification and overall disease. Furthermore, no significant differences between active and placebo were demonstrated in the patients' assessments. In 16 of their 24 patients the eczema was considered related to food allergy. The authors did not find any effect on IgE, RAST or eosinophil count, just as in our study.

No lasting adverse effects were recorded in blood chemistry or urine tests, and no serious side effects were seen in this study.

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