

Topical Sodium Cromoglycate in Atopic Dermatitis

A Disappointing but Informative Trial

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Forty children with atopic eczema requiring topical steroids entered a double-blind group comparative study over 12 weeks and were randomized to either 4% sodium cromoglycate (SCG) in an oil-in-water cream or matching placebo cream. The eczema was evaluated on area charts for 20 parts of the body at five clinic visits. In addition, the families kept diaries on symptoms and treatment. After 3 weeks there were small but statistically significant decreases in severity scores recorded at the clinical visits in the SCG group compared with small increases in the placebo group. However, there were no statistically significant differences in the diary card data during the first 3 weeks of treatment or in any other period, nor were significant differences found in any efficacy data collected during the other 9 weeks of the trial. There were no marked differences in treatment opinions, unusual symptoms, skin infections, use of topical steroids or drugs, or acceptability data between the groups. *Staphylococcus aureus* was found once or twice in cultures from eczema lesions in 31 of 40 children with no marked group difference. The trial showed that there is great need for improved information, family support and topical as well as general treatment in childhood atopic eczema, but topical SCG did not relieve the patients' eczema.

Key words: atopic dermatitis; sodium cromoglycate; children; *Staphylococcus aureus*.

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CLINICAL ASPECTS

Atopic eczema did not significantly improve with topical SCG. Itch and skin infections are great problems. Seasonal variations in severity, attention - placebo effects, concomitant treatment, difficulties in evaluation of severity and acceptability of trial preparation pose problems in trials of topical treatment in atopic eczema.

Atopic eczema is characterized by a dry, itchy skin and a tendency to run within families together with other atopic diseases. Many, but far from all cases, have elevated serum IgE concentrations (16) and many patients, especially young children, show deterioration of the eczema after ingestion of certain foods, notably hen's egg (2,11). The basic mechanism behind the symptomatology is still under debate but the close relationship with bronchial asthma (10) lends further support to an underlying allergic component including possible involvement of skin mast cells. As sodium cromoglycate (SCG) is of definite value in the treatment of bronchial

asthma (1), especially in childhood, it was natural to investigate the possible beneficial effect of topical SCG in atopic eczema. However, in early studies white soft paraffin was used as vehicle and clinical results of these trials were inconsistent (5, 7, 12, 15).

When a 4% cream in an oil-in-water vehicle was made available we started a trial in children suffering from moderately severe steroid-requiring atopic eczema. The purpose was to study whether topically applied SCG was able to reduce symptoms and signs of atopic eczema, especially the itch, if it was possible to reduce the use of topical steroids, and if the number of

skin infections could be reduced. A double-blind group comparative study design was selected with patient allocation at random for 12 weeks' topical treatment with either SCG or placebo.

Although the trial gave a negative result, important information was collected with possible implications for future trials.

MATERIAL AND METHODS

Forty children and adolescents with atopic eczema requiring topical steroids were selected from 135 possible candidates registered at the Pediatric Allergy Clinic (Table 1). All 40 had itch and typical distribution of the eczema, required topical steroids at least once a week at the start of the trial, and had interference with daily life or sleep due to the eczema during up to (but not exceeding) 100 days or nights per year! Patients on oral sodium cromoglycate or oral steroids or with pyoderma were not allowed to enter the study. Written informed consent was given by

the parents of all participants and the study was approved by the Human Research Ethics Committee.

After a 3-week run-in (baseline) period during which previous treatment was continued and registered, the children entered a 12-week double-blind group comparative study. They were randomized to either topical SCG (4% in an oil-in-water cream) or placebo (same cream but no SCG). The composition of the cream comprised colloidal silica, liquid and soft white paraffin, miglyol 812, glycerol monostearate, and cetostearyl alcohol. The trial ointment was to be rubbed into sites of active eczema in the morning and the evening. The families were also given tubes of 1% hydrocortisone ointment which were to be returned after each period. The use of hydrocortisone was registered by recording tube weight loss. The families were instructed to use hydrocortisone only to control exacerbations of the eczema. Concomitant therapy allowed during the trial included antihistamines, to be taken only when necessary, bath oils and emulsifying ointments, and treatment for asthma (except oral steroids). Potent topical steroids were only allowed if badly required and were registered on the diary card together with all other medication.

The families visited the clinic five times at 3-week intervals. Skin prick tests with seven basic food extracts 1:20 (Hollister-Stier) and with further allergens at request of the parents were performed before the trial start. Histamine 1mg/ml was used as a positive reference. The families were interviewed about the skin disease, concomitant diseases, use of drugs and current topical treatment as well as present diet. The interview was repeated at subsequent visits and questions were added regarding possible side effects and change in the eczema since last visit.

Blood was drawn at entry and at the final visit for determination of serum IgE (by Phadebas IgE PRIST®). At all clinic visits, the state of the eczema was recorded on an area chart. Signs were recorded on a 0 to 3 (from none to severe) scale for each of 20 defined body areas. Redness, vesiculations and crusting, excoriations and lichenification, as well as extent of the

Table 1
Patient characteristics by trial group

	SCG	Placebo
Age (years)		
mean	5.6	5.2
range	1-18	1-12
Sex		
male	11	8
female	9	12
Mean duration of atopic eczema (years)	3.9	4.4
Concomitant atopic disease	8	13
Family history of atopic disease	20	19
Currently on a diet	15	19
Positive skin prick test to food	5	10
Positive SPT, inhalants only	4	3
Baseline findings on area charts*		
Redness	0.51	0.46
Excoriation	0.40	0.24
Lichenification	0.66	0.59
Overall mean score	0.41	0.34
Area affected	0.64	0.58

*No significant group difference was found ($P > 0.05$; Mann-Whitney U-test)

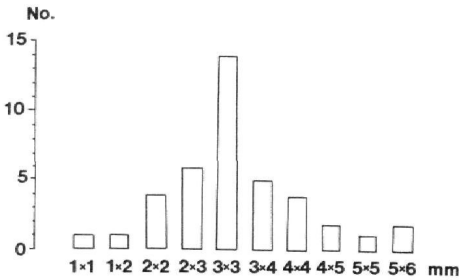


Fig. 1. Wheal sizes with histamine hydrochloride 1 mg/ml

eczema (area affected), were recorded separately.

Bacterial cultures to estimate semi-quantitatively the occurrence of *Staphylococcus aureus* were taken from active eczema sites at entry, at the final visit and when there was pyoderma.

Starting during the baseline period, the families kept a diary at home regarding symptoms and signs and all use of drugs including topical treatment. Itch, sleep disturbance, and overall severity of the eczema, were recorded on a 0 to 3 scale every day. At the last visit, the family's and clinician's opinions of the efficacy of the trial cream were recorded and the family gave their opinion on the acceptability of the trial cream. At the same visit, 30 of the families volunteered to answer, anonymously, questions regarding the trial and their child's eczema and to express wishes concerning future treatment. Mann-Whitney U-tests were used for evaluation of differences during the trial.

Table 2

Comparison of mean area chart scores - differences between week 3 and baseline. NB. All other area chart comparisons showed no significant group differences

	SCG	Placebo	P
Redness	-0.05	0.09	< 0.05
Vesiculation and crusting	0.00	0.00	NS
Excoriation	-0.10	0.00	NS
Lichenification	-0.06	0.07	< 0.01
Overall mean score	-0.06	0.04	< 0.01
Area affected	-0.04	0.10	< 0.05

RESULTS

The randomization established groups with closely corresponding characteristics (Table 1). The most common diet was minus hen's egg (in 18 of the children). Skin tests with histamine 1 mg/ml showed a wide distribution of results, including 12 wheals smaller than 3×3 mm (Fig. 1).

There were three drop-outs, one in the SCG group, due to lack of compliance with the protocol, and two in the placebo group (two families would not continue due to deterioration of the eczema).

No significant difference was found in the family's or the clinician's assessment of the severity of the disease during the last 3 weeks as stated at any visit. Assessments on area charts showed no significant group differences except when comparing the situation 3 weeks after start with baseline ($P < 0.05$ - 0.01 , Table 2). Group differences were less marked during the rest of the trial and none was statistically significant.

Table 3

Mean scores in baseline period and changes in score card recording during weeks 10-12 and baseline period. No significant group differences were found

Variable	SCG	Placebo
Itching at daytime		
baseline	1.35	1.00
change	-0.01	0.10
Itching at night		
baseline	0.94	0.74
change	-0.12	0.01
Sleep disturbance		
baseline	1.00	0.76
change	-0.04	0.01
Overall severity		
baseline	1.51	1.42
change	-0.05	0.02
Use of hydrocortisone		
baseline	1.37	1.26
change	-0.43	-0.47

The mean number of daily applications of hydrocortisone decreased in both groups, but did not differ between the treatment groups during any of the 3-week-periods (Table 3). The total amount of hydrocortisone used was assessed in 12 children from each group and showed no significant difference (mean $\pm$ SD was 76.9 ± 28.5 g in the SCG group and 61.6 ± 51.4 g in the placebo group). Occasional doses of a potent topical steroid were used in two children in the SCG group and in three children in the placebo group. Antihistamines were taken orally during the trial, due to severe itch, by three children in the SCG group and nine in the placebo group. However, the number of doses was small and no significant difference was seen between the groups.

There was no marked difference between the treatment groups in the reporting of unusual symptoms: drier skin was reported twice from the SCG group and both skin irritation and increased itch twice from the placebo group. Pyoderma requiring oral antibiotics was seen in seven children (2 in the SCG group and 5 in the placebo group). Four of these episodes occurred in children with known use of topical steroids: mean 125.5 g (range 90 to 162 g), i.e. well above the mean for the whole group of patients. *Staph. aureus* was found once or twice in cultures from 31 of the 40 children, and in 51 of 84 cultures made during the study period. The number of cultures with *Staph. aureus* was evenly distributed between the groups (22 in the SCG group and 24 in the placebo group when calculating only samples taken at the entry and last visit). There was no significant correlation between the serum IgE concentration and number of positive cultures. Two positive cultures were associated with a slightly (but not significantly) higher use of hydrocortisone (80.3 ± 16.9 g) than one or no positive cultures (65.1 ± 50.4 g).

Serum IgE concentrations were high in both groups - above the geom.mean + 2 SD for age in 34 of 37 children (9). There was no significant group difference in the geom.mean values at start (707 and 656 kU/l, respectively). The mean concentration decreased in both groups during the trial, by approximately 10% in the

SCG group and 26% in the placebo group, but the change did not show any significant group difference (decrease $> 10\%$ in 8 SCG- and 6 placebo-treated children).

The overall severity of the skin disorder, according to the diary cards, showed only minor changes. No significant group differences were found when analysing the diary cards (Table 3). The family's and clinician's opinions at the last visit on treatment effectiveness showed no significant group differences. According to the parents, the eczema in three placebo-treated but none of the SCG-treated children was made worse by the treatment. Both trial creams were well accepted by all but three of the families, and there was no significant difference in the acceptability of the two creams.

From the anonymous questionnaires it was learnt that 16 of the 30 families, in spite of instructions, had intensified the treatment of their child's skin during the trial period - not changing the method of treatment but paying more attention to symptoms and spending more time rubbing in allowed creams and ointments. Otherwise, the instructions were followed by all but two families (who rubbed in the cream only in the evening). All but four felt fully informed about the treatment of eczema prior to the trial and the rest got their information during the baseline period. Nevertheless, almost all families expressed the need for more information on eczema, on the use of topical steroids and other topical and general treatments, and especially on the problems of food intolerance and skin infections.

The trial cream (SCG or placebo) was characterized as softening by 22 of 30 families and

Table 4

The ideal cream for the treatment of eczema

1. Should not smell or discolour.
2. Should not be sticky.
3. Should not increase itch when rubbed in.
4. Should cool the skin.
5. Should take away the itch.
6. Should have long-term effect.
7. Should be safe.

itch-reducing by five families, but seven families complained about increased itching and four found that the creams made the skin more dry. Almost all families treated the child's skin in the morning and the evening. Half the group treated the skin for 3–10 min, the rest for 15–20 min. About 25% of the children were put to bed immediately after the different creams had been applied. The parents felt disappointed that no real itch relief was obtained from use of the trial cream. Parents' requirements for an ideal cream for the topical treatment of eczema are listed in Table 4.

DISCUSSION

The negative results are in agreement with our previous study on topical SCG (10% in white soft paraffin), but at the time the vehicle was blamed for the lack of effect (5). Unlike Haider (7), Zachariae et al. (15) were also unable to show SCG superior to placebo. Our results are consistent with the demonstration that SCG does not modulate human allergic skin reactions when injected intradermally together with ragweed allergen in ragweed allergic subjects (13) or together with codeine (14). SCG appears to stabilize connective tissue mast cells but not mucosal mast cells (4). New drugs with the capacity to block histamine release also from mucosal mast cells should make it possible to assess the role of mast cells in atopic eczema.

The patients who entered the study were carefully selected regarding diagnosis and present state of health, and the trial was run in the off-pollen period of the year. Instructions seem to have been followed reasonably well but, as in all clinical trials, when interest is focused on the symptoms of the patients, the family will also intensify the nursing of the disease. This could, of course, have masked an effect of the active preparation but not to the present extent. The lack of significant findings (with the exception of area chart data 3 weeks after the start compared with baseline) forces us to abandon the hope of treating atopic eczema with topical SCG and to reconsider the histology of normal and eczematous skin, especially concerning the presence of different types of mast cells (3), and

to look more deeply into other possible cells and mechanisms involved in atopic eczema. As judged from skin prick test results the need for a diet at the time of study was overestimated by the parents of more than half the group (19 of 34 children) currently on a diet.

Staph. aureus was found abundantly as expected (6), but the treatment given for overt pyoderma could not have contributed to the overall result of the trial. The moderate decrease in serum IgE concentrations could perhaps mirror an improvement in the state of the eczema during an intensified treatment (8), but could also be explained by a seasonal variation of IgE related to respiratory atopic diseases in the children.

We learnt from the study that the improvement which most children with atopic eczema experience during the summer is still influencing their state of health during September to November, as more than half of the group initially considered for the study did not fulfil the inclusion criteria at clinical investigation. On the other hand, we feel that a trial in atopic eczema needs a long run-in period to reduce attention - placebo effects, and, as a consequence, such trials are difficult to perform.

Skin infections requiring oral antibiotics were common, occurring in seven of 40 children during the 15 weeks' trial. Evaluation would have been even more difficult if we had studied children with severe eczema who probably have even more frequent episodes of overt skin infections.

Evaluation of treatment of eczema should focus on objective measurement of the itch and on the use of other itch-reducing therapy. Area charts for recording severity and extent of eczema seem worthwhile, but the skin should be divided into more than 20 areas for the demonstration of possible differences in extent of the eczema, or careful examinations of one or two well-defined areas should be selected for evaluation. Furthermore, papules and pustules should also be recorded, or a trial should focus only on signs of the patient's scratching. Naturally, a trial in eczema must be performed under double-blind conditions as in the present study.

The results of the questionnaire confirmed that atopic eczema in a considerable number of

children is still a functionally impairing disease, that the families of such children need a lot of information and support, and that there is a need for further improvement of topical and general treatment of atopic eczema.

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