

## **The effect of orally administered sodium cromoglycate on symptoms of food allergy**

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### **Summary**

A comparison was made between the effects of sodium cromoglycate (SCG) and placebo on symptoms of food allergy in twenty children. Both the clinician's and patient's preferences and the clinician's evaluation of the specific response to challenge showed a significant benefit from SCG. A striking effect on skin symptoms was seen in some children and the recorded mean score for skin symptoms was lower after 2 weeks' treatment with sodium cromoglycate. However, the differences detected from the mean symptom scores were not statistically significant. Neither were there any significant changes in the IgE, IgG, IgA and IgM food allergen antibody levels related to the treatment.

### **Introduction**

The efficacy of SCG in allergic disease has been ascribed to its ability to prevent reagin induced mediator release. The drug is already widely used in prophylactic therapy of bronchial asthma (Altounyan, 1967; Pepys *et al.*, 1968), allergic rhinitis (Blair & Herbert, 1973) and encouraging results are also reported with orally administered SCG in gastrointestinal disorders such as gastrointestinal allergy (Kingsley, 1974), cow's milk allergy (Freier & Berger, 1975; Kuzemko & Simpson, 1975), chronic proctitis (Heatley *et al.*, 1975), ulcerative colitis (Mani *et al.*, 1976), and diarrhoea in chronic mastocytosis (Dolowich *et al.*, 1974) and, in addition, in chronic infantile eczema (Russel & Shaw, 1975). The drug is regarded to be almost non-toxic and it is resorbed through the gut wall to a very small extent (Walker *et al.*, 1972).

Promising results indicating a beneficial effect of SCG on the symptoms of food allergy in single patients observed by us and others have encouraged the present double-blind cross-over study. Its aim was to investigate the efficacy of orally administered SCG in preventing symptoms of food allergy in childhood and to analyse the possible influence of SCG treatment on the levels of certain food antibodies during diet and challenge.

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## Material and methods

### Patients

Twenty children, ranging in age from 1 to 15 years, with a diagnosis of food allergy according to history, were selected for the trial. Most children had a long history of allergic illness with eczema and asthma as the dominating symptoms. The children were allergic to a wide variety of foods of which the most common are recorded in Table 1. On challenge with these foods the most common manifestations were eruption of eczema, urticaria, circumoral rash and itching (ten patients), but also gastrointestinal

**Table 1.** The most common foods causing allergic symptoms, foods taken during challenge and frequency of positive RAST to egg, fish and milk

|                  | Food causing<br>allergic symptoms | Foods to be taken<br>during challenge | RAST positive |
|------------------|-----------------------------------|---------------------------------------|---------------|
| Egg              | 11                                | 9                                     | 12            |
| Fish             | 6                                 | 5                                     | 5             |
| Fruit/Nut        | 10                                | 3                                     | NT            |
| Vegetables       | 8                                 | 5                                     | NT            |
| Milk             | 2                                 | 1                                     | 4             |
| Chocolate        | 3                                 | 1                                     | NT            |
| Dyes, Penicillin | 4                                 | 0                                     | NT            |

symptoms were common (eight patients), and asthma occurred only in six fish allergic children. The children under study were skin test positive to food allergens in most instances. Only two patients were free from symptoms on elimination diet during the trial. Some children had intercurrent infections in the respiratory and gastrointestinal tract, but it was not necessary to interrupt the SCG or placebo medication.

Four patients did not conform to protocol and were excluded from the analysis. Two of them did not take the drugs as prescribed. One patient was withdrawn during the SCG treatment because of urticaria and one patient was withdrawn during placebo treatment because of increased symptoms. This child was already on oral SCG before the trial and he seems to need continuous SCG treatment to be asymptomatic. Hence sixteen patients were included in the analysis.

### Design of the trial

The trial was carried out as a double-blind cross-over trial in which the active treatment was SCG and the placebo was glucose, both given orally, dissolved in 10 ml of water, at a dose of 100 mg four times a day 30–60 min before meals. Each patient entering the trial was allocated at random to a drug sequence (SCG–placebo or placebo–SCG) (Fig. 1) and received treatment with SCG and placebo, each for a period of 3 weeks. For the third week of the two treatment periods, the parents were instructed to give the child a food to which the child was allergic in quantities usually sufficient to give symptoms. The clinician was continuously informed and decided if the food should be given again the following day or if the amount was to be increased. Thus, the number of days during which the children were challenged varied from 1 to 7

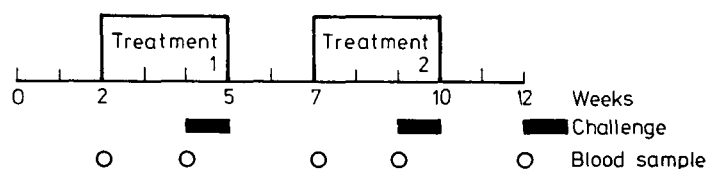


Fig. 1. Design of the trial.

days (Table 1). Following the first treatment period there was a 2-week wash-out period during which the child reverted to the ordinary elimination diet and then commenced a second 3-week treatment period with the alternative treatment. Diary cards were completed by the parents with daily recordings on a four point scale (0–3) of the severity of three different kinds of symptoms from the skin, respiratory and gastrointestinal tract. On the basis of symptoms reported daily after each challenge the response to the food challenge was recorded by the clinician on a four point scale (0–3). At the end of the trial, preferences by both the clinician and the parents were recorded. The patients were examined and venous blood samples were drawn five times during the trial (Fig. 1). Sera were stored at  $-20^{\circ}\text{C}$  until analysed.

#### Laboratory investigations

IgE concentrations were measured by a direct sandwich type of radioimmunosorbent technique, PRIST (Ceska & Lundkvist, 1972; Johansson *et al.*, 1976). The IgE antibody activity was determined by the radioallergosorbent test, RAST (Johansson *et al.*, 1971). Allergens used were  $\beta$ -lactoglobulin (Miles Laboratories Ltd, lot. no. 48-96002-4), ovomucoid from raw egg white (Miles Laboratories Ltd, lot. no. 8-96016) and purified fish allergen, DS22 (Aas, 1967; kindly supplied by Dr Kjell Aas). IgG antibodies to the same allergens were measured by a method based on the binding of IgG antibody to staphylococcus protein A coated Sepharose (Johansson *et al.*, 1976), as described in detail (Foucard & Johansson, 1976) using  $^{125}\text{I}$ -labelled allergens. IgA- and IgM-antibodies were measured by the same technique, using Sepharose beads coated with anti-IgA and anti-IgM, respectively.

Table 2. Parents' preferences at the end of the trial. ( ) = clinician's preferences

|              | Preferred |         | No preference |
|--------------|-----------|---------|---------------|
|              | SCG       | Placebo |               |
| SCG-placebo  | 7         | 1       | 1             |
| Placebo-SCG  | 4         | 1       | 2             |
| All patients | 11 (10)   | 2       | 3 (4)         |

#### Results

At the end of the trial both the clinician and the parents were asked to state a preference for either treatment period. As seen in Table 2 for parents' preferences, eleven were in

**Table 3.** Mean challenge score from recordings by the clinician during the third week of treatment

|              | SCG | Placebo | <i>t</i> -value | Significance    |
|--------------|-----|---------|-----------------|-----------------|
| SCG-placebo  | 1.3 | 2.1     | 5.5 (7)         | N.S.            |
| Placebo-SCG  | 1.0 | 1.6     | (No; too small) |                 |
| All patients | 1.2 | 1.9     | 8 (10)          | <i>P</i> = 0.05 |

**Table 4.** Mean symptom scores during the challenge week

|            | SCG  | Placebo | <i>t</i> -value* | Significance |
|------------|------|---------|------------------|--------------|
| Skin       | 11.2 | 12.8    | 15 (10)          | N.S.         |
| Nose       | 1.6  | 2.4     | (No; too small)  |              |
| Lung       | 3.0  | 4.1     | (No; too small)  |              |
| G.I. tract | 3.2  | 6.1     | 17 (11)          | N.S.         |
| Total      | 19.6 | 25.4    | 33.5 (14)        | N.S.         |

\* Wilcoxon matched pairs signed rank test (untied pairs).

**Table 5.** Laboratory data: medians and ranges of tested parameters at the beginning and at the end of each treatment period and at the end of the trial. IgE antibody titres are expressed in PRU (Phadebas® RAST unit), IgG antibody titres are expressed as percentage (%) of the titre in a serum pool from healthy blood donors and IgA antibody titres as percentage (%) of a reference serum

| Allergen                             | Antibody type | SCG               |                   | Placebo            |                    | Week 12           |
|--------------------------------------|---------------|-------------------|-------------------|--------------------|--------------------|-------------------|
|                                      |               | Beginning         | End               | Beginning          | End                |                   |
|                                      | IgE (kU/l)    | 155<br>(13-1100)  | 350<br>(13-1000)  | 190<br>(12-850)    | 290<br>(55-850)    | 260<br>(15-2400)  |
| Ovomucoid                            | IgE           | 0.2<br>(<0.1-2.5) | 0.3<br>(<0.1-5.5) | 0.2<br>(<0.1-6.5)  | 0.5<br>(<0.1-6.0)  | 0.4<br>(<0.1-5.3) |
|                                      | IgG           | 11<br>(3-430)     | 15<br>(3-388)     | 11<br>(1-350)      | 13<br>(2-350)      | 18<br>(7-300)     |
|                                      | IgA           | 7<br>(<1-46)      | 8<br>(<1-44)      | 10<br>(<1-47)      | 7<br>(<1-41)       | 8<br>(<1-44)      |
|                                      | IgE           | <0.1<br>(<0.1-41) | <0.1<br>(<0.1-48) | <0.1<br>(<0.1-0.2) | <0.1<br>(<0.1-46)  | <0.1<br>(<0.1-46) |
| β-Lactoglobulin                      | IgG           | 4<br>(<1-124)     | 4<br>(<1-45)      | 4<br>(<1-133)      | 3<br>(<1-129)      | 4<br>(<1-119)     |
|                                      | IgA           | <1<br>(<1-51)     | <1<br>(<1-16)     | <1<br>(<1-60)      | <1<br>(<1-59)      | <1<br>(<1-41)     |
|                                      | IgM           | 3<br>(<1-133)     | 3<br>(<1-21)      | 2<br>(<1-152)      | 4<br>(<1-149)      | 4<br>(<1-92)      |
|                                      | IgE           | <0.1<br>(<0.1-86) | <0.1<br>(<0.1-95) | <0.1<br>(<0.1-85)  | <0.1<br>(<0.1-100) | <0.1<br>(<0.1-78) |
| DS 22<br>(purified fish<br>allergen) | IgG           | 3<br>(<1-180)     | 4<br>(<1-160)     | 4<br>(3-200)       | 4<br>(2-190)       | 4<br>(2-170)      |

favour of the SCG period ( $P < 0.05$ ). Similarly the clinician's preference was significantly ( $P < 0.05$ ) in favour of the SCG period.

The mean symptom scores for the first 2 weeks of each treatment period showed no significant difference between SCG and placebo but in five children a remarkable relief of skin symptoms was seen during SCG treatment. On challenge a lower mean challenge score was achieved during SCG treatment compared to placebo ( $P = 0.05$ ) (Table 3). The mean symptom score for the week during which allergen was taken was lower for the SCG period but the difference from the placebo was not significant (Table 4).

#### *Laboratory findings* (see Table 5)

The IgE level was raised in all children (geometric mean 340 u/l). During the trial the levels increased but this could not be correlated to SCG or placebo treatment. IgE antibodies to  $\beta$ -lactoglobulin, ovomucoid and fish (DS 22) were detected in most patients with symptoms caused by these allergens (Table 1). Changes of IgE antibody levels during the trial could not be correlated consistently with treatment or challenge periods.

Most patients also had food antibodies of the G, A and M immunoglobulin classes. The highest levels were found in patients who also had IgE antibodies to the same allergen. No significant difference in titres was found between samples obtained at different times during the trial. Several patients had increased titres after challenge with some of the tested foods, but there was no significant difference between titres after the SCG and after placebo treatment. The greatest variation in antibody titres was seen in some patients who had intercurrent infections with asthmatic episodes or diarrhoea. In these children all the IgE level and the IgE-, IgG- and IgA-antibody titres to the tested foods increased in parallel despite treatment and strict elimination diet.

#### *Side effects*

In this study only one patient experienced an unwanted reaction that may have been the result of the treatment given. This was a girl who developed transient urticaria after 2 weeks' treatment with SCG. When SCG was withdrawn for 24 hr the urticaria disappeared but reappeared after another dose of SCG. The patient excluded from this study because of deterioration during placebo treatment showed convincingly a protective effect by oral SCG on the symptoms of food allergy. This 7-year-old boy, with proven hypersensitivity to animal danders, house dust, pollens and several foods, suffers from asthma, eczema and relapsing kerato-conjunctivitis. His food allergy is so broad and severe that it is difficult to find a diet he can tolerate. He was started on oral SCG 2 years ago with rapid improvement. During SCG treatment his diet is less strict and he can take 1 glass of milk without a flare up of his symptoms. Only 2 days after stopping SCG medication a few millilitres of milk caused a flare up of the keratoconjunctivitis and asthma. This increased tolerance to offending foods during SCG treatment has been repeatedly proven and made it possible for the family to recognize immediately the placebo period in this trial.

#### **Discussion**

Adverse reactions to foods are common in children. The underlying mechanisms are to a great extent unknown. Allergy, a designation that should be used for immuno-

logical reactions only, is in some children a prominent clinical problem. Despite strict diets, eliminating all suspected offending foods, the child is never entirely symptom free and in patients allergic to several basic foods nutritional problems may occur. The successful treatment with oral SCG of a 7-year-old boy with pronounced food allergy, called for a critical investigation of the possible protective effect of SCG in children with food allergy. Children with food allergy symptoms of the immediate type were treated by SCG in a double-blind cross-over study. The results show a significant preference in favour of SCG over placebo by both patients and the clinician. During the week when the children were challenged with food that they did not tolerate normally there was a higher mean symptom score for placebo than for SCG treatment but the difference was not statistically significant. The allergy symptoms on challenge were often of short duration, most having disappeared within 24 hr. Since most of the children were not challenged every day of the week it is not surprising that these specific effects could not be detected from the broad symptoms defined on the diary cards and given as a mean weekly score. The response to challenge as seen in the challenge score is more evident and is significantly in favour of a therapeutic effect of SCG ( $P = 0.05$ ).

It seems reasonable to assume that SCG can decrease and sometimes prevent symptoms of food allergy in atopic RAST-positive children. Only five children in this study had a negative RAST to all tested allergens and only one of them recorded relief of symptoms and preference in favour of SCG. The mechanism for the beneficial effect of SCG is unknown but the very small resorption of SCG speaks in favour of a local effect on the intestinal mucosa. It has still to be ascertained whether SCG is able to decrease or prevent a release of mediators from sensitized mast cells in the intestine, thereby reducing gut permeability for food allergens.

No consistent changes in the serum levels of food antigen antibodies of any immunoglobulin class were found. These findings may mean that SCG has little influence on the immunological mechanisms of food allergy or that the food antibodies in the serum are not related to the disease. However, the most likely explanation is that the duration of the periods of treatment with or without food challenge were too short to allow any significant changes to occur.

Unwanted reactions to inhaled SCG occur rarely but skin eruptions and pulmonary infiltrates have been reported (Löbel, Machtey & Eldror, 1972; Sheffer, Rocklin & Goetzl, 1975). Side effects from oral administration have not been reported. However, one case with urticaria which repeatedly occurred after administration was possibly an adverse reaction to SCG, although other factors could also have been involved.

The results of this study indicate that oral SCG may have a place in the treatment of IgE-mediated food allergy in childhood, especially in patients who have an extreme allergy to basic foods and symptoms which continue despite elimination diets.

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