

Nebulised Sodium Cromoglycate in the Treatment of Wheezy Bronchitis

A Multicentre Double-Blind Placebo Controlled Study

A. BERTELSEN,¹ J. B. ANDERSEN,¹ P. BUSCH,² P. DAUGBJERG,³ B. FRIIS,⁴
L. HANSEN,⁵ S. V. JACOBSEN,⁶ I. PELCK,⁷ W. PETERSEN,⁷ P. PRAHL,⁴
O. ØSTERBALLE⁵ and G. Z. ØSTERGAARD²

Department of Paediatrics, ¹Frederiksborg Amts Centralsygehus, Hillerød, ²Amtssygehuset, Roskilde, ³Sundby Hospital, ⁴Københavns Amts Sygehus, Gentofte, ⁵Viborg Sygehus, ⁶Børnehospitalet, Fuglebakken, and ⁷Rigshospitalet, Denmark

The efficacy of nebulised sodium cromoglycate (SCG) used as a prophylactic treatment of wheezy bronchitis in children aged 1 to 4 years was evaluated in a multicentre double-blind placebo controlled, group comparative study. Fifty-four patients completed the 10-week trial (29 treated with SCG and 25 treated with placebo), preceded by 4-8 weeks baseline. Nebulised SCG did not prove significantly superior to placebo in reducing day wheezing, day coughing, or sleep disturbance due to wheezing or coughing at night. Neither was there significant difference in the use of supportive medicine (β_2 -agonist and theophylline) between the groups. Extra doctor visits, hospital admissions, and parental preference did not show significant difference either.

Key words: atopic children; coughing; nebulised bronchodilator; nebulised sodium cromoglycate; prophylaxis of wheezy bronchitis; sodium cromoglycate (SCG); wheezing; wheezy bronchitis.

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CLINICAL ASPECTS

Sodium cromoglycate (SCG) is widely used as a prophylactic medication in wheezy bronchitis in young children. In this study SCG did not prove superior to placebo.

Many children suffering from recurrent wheezy bronchitis need prophylactic treatment. In some centres nebulised sodium cromoglycate (SCG) is used, possibly combined with a bronchodilator.

In adults and children (age 3-5 years and more) it has appeared that SCG has a prohibiting effect on asthma induced by cold air, exercise, sulphur dioxide, and allergen challenge (1). Small children with wheezy bronchitis, however, form etiologically a somewhat different group of patients, since their symptoms may, besides the above mentioned, more often be induced by airway infections (3, 6). Some controlled investigations of the prophylactic effect of SCG in this young group of children are available (2, 4, 5, 7, 9, 10, 11), but a

number of these are based on less than 25 patients (2, 5, 7, 9), and include somewhat older children (5, 7, 9, 10, 11).

The aim of this study was to compare the efficacy of nebulised SCG and placebo as a prophylactic treatment of wheezy bronchitis in young children (age range 1-4 years) in a larger number of patients than studied by previous investigators.

MATERIAL AND METHODS

Patients

Fifty-nine patients aged 1 to 4 years (mean 25.5 months in the SCG group, and 25.1 months in

the placebo group) entered the study. The patients were randomly assigned to the active ($n = 31$) and the placebo ($n = 28$) groups. Fifty-four patients completed the trial, 29 treated with SCG and 25 with placebo. Two patients from the SCG group were withdrawn from the trial, one failed to cooperate and one had a severe pneumonia. Three patients from the placebo group were withdrawn, two failed to cooperate, one suffered severe daily symptoms of wheezy bronchitis.

All children had had recurrent wheezy bronchitis demanding therapy at least once a month during the preceding winter or later. Twelve children in the SCG group and nine in the placebo group had had symptoms at least weekly. Before entering the study, the SCG group had a total of 87 hospital admissions, the placebo group 97 hospital admissions due to wheezy bronchitis.

On entering the study none of the children had fever or signs of pneumonia, and none received prophylactic treatment for wheezy bronchitis. None of the children had chronic diseases of the airways, or required additional medicine continuously.

Twenty-eight patients had at least one first-degree relative with allergic type-I disease (14 SCG, 14 placebo). Twenty-seven children were looked after in kindergarten (13 SCG, 14 placebo), 17 in private homes (9 SCG, 8 placebo) and 15 in their own homes (9 SCG, 6 placebo). Forty-seven children lived in a dry and warm house/apartment (26 SCG, 21 placebo). Tobacco was smoked in the home of 21 children in the SCG group and 21 in the placebo group.

Parents gave informed consent to their children entering the study.

Methods

The trial was a multicentre, double-blind group comparative study, carried out during two winter seasons.

The trial was preceded by a 4–8 weeks baseline period, where no prophylactic treatment was given, patients being allowed to take bronchodilator mixture, and theophylline supposi-

tory in normally prescribed doses. A few of the patients, earlier receiving nebulised bronchodilator during acute attacks of wheezing, were allowed to have this treatment during the baseline period.

The treatment period lasted 10 weeks, the patients receiving either SCG solution 20 mg (equals 2 ml) or placebo 2 ml three times daily, nebulised by Pari or Optimist inhaler. In cases of more than 30 min of wheezing, nebulized β_2 -agonist, supplemented by theophylline suppository if needed, was given.

During the baseline period the frequency of symptoms and the cooperation of the patients was assessed and the parents made familiar with the diary cards which were completed throughout the study. On a 0–3 scale of increasing severity the following symptoms were recorded: day wheezing, day coughing, sleep disturbance due to wheezing and coughing at night. Additional treatment with bronchodilators and theophylline was recorded, as well as extra doctor visits, hospital admissions, other significant events, and possible side effects. At the end of the trial, parents' assessment of treatment effect was stated.

Patients were assessed clinically before and after the baseline period and after 2, 6 and 10 weeks of therapy. On entering the trial, the following investigations were made: Chest X-ray, total IgE (Pharmacia, Prist), RAST (dust mite, cat, cow milk and possible other relevant allergens) (Pharmacia RAST), IgA, IgG, IgM, α_1 -antitrypsin and sweat test.

A 5% two-tailed significance level was used in all statistical tests. Diary card scores and use of extra bronchodilators/theophylline were analysed using the Mann-Whitney U-test. Extra doctor visits, hospital admissions and parents' assessment of treatment effect were analysed using Fisher's Exact Test.

RESULTS

Table 1 shows the daily mean scores during the baseline and the treatment period for the SCG and placebo groups, whereas Fig. 1 shows the difference in daily mean score between baseline and treatment period for all patients. Both

treatment groups had fewer symptoms during the treatment period than during the baseline period, the difference between SCG and placebo not being statistically significant for either day wheezing, day coughing or sleep disturbance due to wheezing or coughing.

Fig. 2 a and b show use of supportive medicine in all patients during the treatment period, expressed as mean number of doses per day. Since the patients mainly used mixture during the baseline, but nebulised β_2 -agonist during the treatment period, we have not looked upon the difference between the baseline and the treatment period as far as this point is concerned. Patients treated with SCG did not use significantly lower doses of medicine than did the placebo group.

There was no significant difference between the two treatment groups as for number of children having extra doctor visits. During the baseline period six patients from the SCG group and 11 from the placebo group were hospitalized once. During the treatment period 11 patients from the SCG group were hospitalized once, whereas seven from the placebo group were hospitalized once, one patient twice and two patients three times. This difference is not statistically significant. At the clinical assessments during the trial the frequency of stethoscope examination abnormalities (ronchi, rattling, wheeze, prolonged expiration) showed a decreasing tendency during the treatment period, but without significant difference between the treatment groups.

Chest X-ray, IgA, IgG, IgM, α ₁-anti-

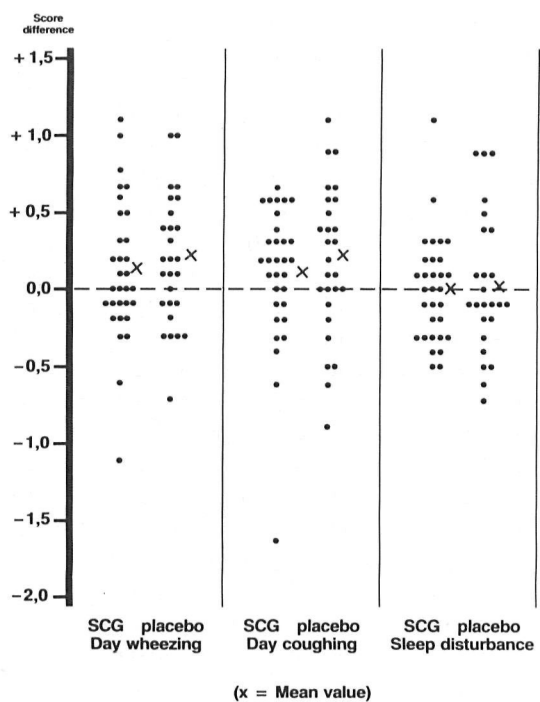


Fig. 1. Difference in daily mean score between baseline and treatment period (baseline-treatment period).

trypsin and sweat test were within normal limits in all patients.

Eighteen patients treated with SCG and 11 patients from the placebo group were classified as atopic, using the criteria: total IgE > 69 U/ml (> 2 SD from the normal mean value of this age group) (8), and/or RAST test class 2 or more. Neither in this subgroup of atopic children did SCG prove significantly superior to

Table 1
Daily mean score during baseline and treatment period

Symptom	Period	Daily mean score (range)		Significance
		SCG	Placebo	
Day wheezing	Baseline	0.51 (0.00-1.90)	0.82 (0.00-2.50)	$P < 0.1$
	Treatment	0.38 (0.00-1.80)	0.64 (0.00-1.80)	NS
Day coughing	Baseline	0.73 (0.00-1.40)	0.89 (0.10-2.20)	NS
	Treatment	0.63 (0.00-2.70)	0.72 (0.00-1.50)	NS
Sleep disturbance	Baseline	0.38 (0.00-1.10)	0.55 (0.00-1.70)	NS
	Treatment	0.38 (0.00-1.30)	0.54 (0.00-1.60)	NS

Mann-Whitney U-statistic.

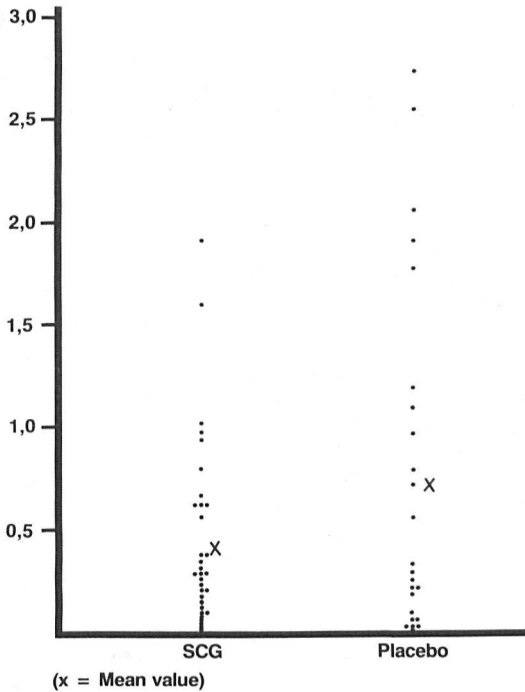


Fig. 2a. Use of B_2 -agonist during treatment period. Mean number of doses per day.

placebo, as far as any of the above mentioned data are concerned.

Possible side effects, including cough in connection with inhalation, were seen in one SCG-treated child and in three placebo-treated children. Inhaling SCG, one patient had eczema around the mouth.

DISCUSSION

Our results are in accordance with those of Dalene (2) and partly with those of Glass et al. (5) whose studies comprised children 1 year 6 months – 4 years of age, and 1 year 9 months – 4 years 5 months of age (mean 3 years 5 months), respectively. Geller-Bernstein et al. (4) noted the same results in children less than 12 months of age, but in contrast found nebulised SCG significantly superior to placebo in children aged 12 to 24 months (mean 17.3 months). However, this age group only comprised 24 patients, and the effect of SCG was only valid concerning the symptom scores,

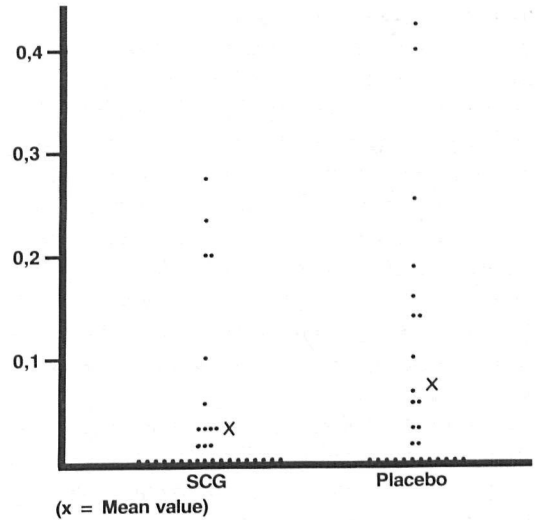


Fig. 2b. Use of theophylline suppository during treatment period. Mean number doses per day.

whereas the use of supportive medicine did not prove any significant difference.

Some authors have used four inhalations a day (2, 4, 5, 9, 11), others three (7, 10). Our patients inhaled three times a day, which is every 4–5 h during daytime with a longer pause during night. If this had been insufficient, one might expect an increase in symptoms during the night, which was not the case. Therefore our treatment schedule seems to be acceptable. Apart from which, patient compliance would rapidly decline with more than three inhalations a day.

The results of the different studies may be influenced by the proportion of the patients being atopic. In the trials showing a beneficial effect of SCG, the majority of the patients were allergic (4, 7, 10), whereas in our study only 29 of the 54 patients who completed the trial were defined as atopic. It is usually difficult to define atopic children in this young age group. However, using the earlier mentioned criteria, in our study atopic children did not seem to have any better effect of nebulised SCG than the rest of the children.

In this study nebulised SCG did not prove significantly superior to placebo in the treatment of wheezy bronchitis, although a slight

tendency in favour of SCG was noted. However, both SCG- and placebo-treated children showed fewer symptoms during the treatment period than during the baseline period. This indicates a considerable placebo effect, as also noted by other authors. This placebo effect may in part be due to the regular humidifying effect of nebulised solution, and to the better effect of the nebulised bronchodilator used as supportive medicine, than of the mixture previously used. Moreover, the additional supervision and concern associated with the study may contribute to the placebo effect.

We conclude that under the conditions of this study, nebulised SCG did not prove better than placebo as a prophylactic treatment of wheezy bronchitis.

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Address:

Dr. Anne Bertelsen
Carinaparken 25
DK-3460 Birkerød
Denmark

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