

Sodium cromoglycate as a replacement for inhaled corticosteroids in mild-to-moderate childhood asthma

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We investigated whether sodium cromoglycate 10 mg three times daily, delivered as an aerosol via Nebuhaler (in addition to terbutaline 0.5 mg three times daily), could replace inhaled steroid in children with mild-to-moderate asthma. Children (mean age 10.3 years) were randomly allocated to 12-week treatment with sodium cromoglycate 10 mg plus terbutaline 0.5 mg (group A; $n=30$) or placebo plus terbutaline 0.5 mg (group B; $n=32$), both taken three times a day. The daily steroid dose was reduced by 50 µg/week for 4 weeks from a starting dose of 200 µg. Fewer patients withdrew owing to worsening asthma from group A ($n=1$) than group B ($n=11$). Symptom scores, morning and evening peak flows, and additional β_2 -agonist usage, recorded on diary cards, were better in group A than group B. Lung function measured at clinic visits was unchanged in either group. Overall opinions of efficacy favoured Group A. Adverse events were similar in the groups. Sodium cromoglycate plus terbutaline substituted effectively for inhaled steroid therapy.

W. Petersen¹, F. Karup-Pedersen², B. Friis³, P. Howitz⁴, F. Nielsen⁵, L.-H. Strömquist⁶

¹Københavns Amts Sygeshus i Gentofte, Hellerup, Denmark; ²Rigshospitalet, Copenhagen, Denmark; ³Roskilde Amts Sygehus, Roskilde, Denmark; ⁴Esbjergs Centralsygehus, Esbjerg, Denmark; ⁵Sønderborg Sygehus, Sønderborg, Denmark; ⁶Innovex Nordic AB, Uppsala, Sweden

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Dr L.-H. Strömquist
Innovex Nordic AB
Dragarbrunnsg. 31
S-753 20 Uppsala
Sweden

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It has become increasingly evident in recent years that even mild and newly diagnosed asthma is characterized by profound inflammatory changes in the airways (1, 2). Thus, recent treatment guidelines (3) recommend that daily inhaled anti-inflammatory therapy should be administered very early in the development of the disease. Two possible treatment options are inhaled corticosteroids and sodium cromoglycate. The inhaled corticosteroids are extremely effective anti-inflammatory agents (4), but even by the inhaled route they are not without systemic side-effects (5, 6). Because of its lack of serious side-effects, sodium cromoglycate is recommended as the first choice for anti-inflammatory treatment in children (3, 7). Since inhaled corticosteroids are widely prescribed in this position, we were interested to examine the feasibility of replacing inhaled corticosteroids with sodium cromoglycate in children with mild-to-moderate asthma. Terbutaline was added to the test treatments in order to reduce the risk of asthma exacerbation during the trial.

Material and methods

Patients were selected from children aged 5–15 years who were attending the physician responsible for the study at each centre. They had to have been receiving an inhaled steroid at a dose of 200 µg/day via a standard metered-dose inhaler for at least 1 month before entry to the study. The children were to be diagnosed as having mild-to-moderate asthma (at least 20% reversibility of peak expiratory flow [PEF] after inhaled β_2 -agonist and a forced expiratory volume in 1 s [FEV₁] of at least 80% of the predicted normal value for their age and height). Their ability to use a pressurized aerosol and spacer (Nebuhaler) to record PEF, and to complete a diary card correctly was checked, and informed consent was obtained.

We excluded patients who had received short courses of oral steroids more than twice or high-dose inhaled steroids on more than 2 days during the preceding 6 months, or sodium cromoglycate during the 4 weeks before entry. We also excluded

patients receiving oral β_2 -agonists, theophylline, or antihistamines. Rhinitis drugs (antihistamines, intranasal steroids, or sodium cromoglycate) were permitted. Respiratory infection during the 4 weeks before entry and significant renal, hepatic, or cardiovascular disease also precluded entry into the study.

This was a double-blind comparison of two treatment groups, one of which received placebo as a control. During a 2-week baseline period, patients familiarized themselves with the procedures of measuring PEF and recording symptoms and additional β_2 -agonist usage each day on a diary card. They were then assigned by a randomization code according to standard statistical tables to treatment with either sodium cromoglycate 10 mg (two puffs from a metered-dose inhaler delivering 5 mg per puff) or matching placebo, taken three times daily via an aerosol and Nebuhaler. The placebo aerosol contained the same propellants and excipients as the sodium cromoglycate aerosol but no active substance, and was identical in external appearance. Both groups also received the inhaled β_2 -agonist, terbutaline, 0.5 mg three times daily via pressurized aerosol, during the trial in order to reduce the risk of asthma exacerbation which might be precipitated by steroid withdrawal.

The test treatments were given for 12 weeks, during which time patients recorded their symptoms, use of rescue β_2 -agonist, and morning and evening PEF each day on diary cards. Each of the daytime (cough, wheeze, and breathlessness) and nighttime symptoms (cough and wheeze) was graded on a scale of severity of 0 = none, 1 = mild, 2 = moderate, or 3 = severe. PEF was recorded as the highest of three consecutive measurements, and inhaled bronchodilator use in addition to that specified by the protocol was recorded as the number of inhalations each day and night. The brand and unit dose of the rescue bronchodilator were kept constant for each patient throughout the study. Patients visited the clinic at the start and end of the baseline, and at treatment weeks 2, 4, 8, and 12, when lung function (PEF, FEV₁, and forced vital capacity [FVC]) were measured and any adverse events recorded. At the final visit, both patients and physicians assessed the overall efficacy of the treatment regimen on a scale of effectiveness of 1 = very, 2 = moderately, 3 = slightly effective; 4 = no effect; or 5 = made condition worse.

All patients were receiving inhaled steroids at a dose of 200 μ g/day on entry and during the baseline period. The dose was withdrawn in steps of 50 μ g/week during the first 4 weeks of treatment. Patients whose asthma worsened during the treatment period were regarded as treatment failures and withdrawn from the trial. Worsening asthma was

defined as need for oral or parenteral steroids, inability to tolerate reduction of the inhaled steroid dose, reduction in PEF to below 50% of the patient's normal value for more than 24 h, or need for parenteral bronchodilators for emergency treatment.

The study design was approved by the hospital ethics committee and was carried out according to the Declaration of Helsinki. The purpose of the trial was explained to all patients and/or their parents, and informed consent was obtained.

The primary variables for defining treatment efficacy were the diary card data, the patients' opinion of efficacy, and the withdrawal rate. Lung function recorded at clinic visits and physicians' overall opinions of efficacy were secondary variables. Mean values for diary card data were calculated for each 2-week period. The primary period for analysis was from baseline to the final 2 weeks of treatment, although results for each 2-week period were also analysed. In the case of withdrawals or data missing for other reasons, the last value was carried forward for the analysis. This avoided the risk of biasing the results in favour of the treatment group with the most withdrawals (if the withdrawal rates were unbalanced) or of overestimating the true group differences by extrapolation. The statistical analyses were performed on the total sample, but the possible effect of centre as a factor could not be tested due to insufficient number of patients in some centers. The effects of the two treatments were compared by Student's *t*-test for all lung-function measurements and the diary card symptom scores. The variable rescue β_2 -agonist use had a skewed distribution; therefore, the treatment groups were compared by the non-parametric Mann-Whitney U-test. Changes from baseline were compared. Differences in withdrawal rate and overall opinions of efficacy were analysed by the log-rank test for comparing two survival curves. Probabilities of 5% or below, by two-tailed tests, were considered statistically significant.

Results

Sixty-eight patients entered the study (two, eight, nine, 19, and 30 at each of the five centres). Five patients were withdrawn before entry to the double-blind phase. Sixty-three patients (31 in group A and 32 in group B) were included in the analysis of safety data. The additional patient in group A experienced dizziness, was withdrawn after receiving test treatment for less than 7 days, and was not included in the efficacy analysis.

Data from 62 patients were available for the efficacy analysis, 30 in group A and 32 in group B. Beclomethasone dipropionate (BDP) was used by

29 children and budesonide by the remaining 33. The groups were well matched apart from the baseline asthma severity, which was slightly greater in group A ($P=0.07$). Table 1 shows further details. At the end of the baseline period, two patients had predicted FEV₁ values slightly lower than the 80% entry criterion. On the basis of clinical judgement, both patients were allowed to enter the treatment phase (one in each treatment group) and were included in the efficacy and safety analyses.

The disposition of the patients during the study is set out in Table 2. The rate of withdrawal due to worsening asthma was significantly different between the groups: one patient (3.3%) from group A versus 11 patients (34.4%) from group B. The rate of asthma deterioration was defined as gradual or sudden on the basis of clinical judgement. When patients were withdrawn, the efficacy data recorded or collected at their final visit were carried forward and used for the remaining analyses at each time point.

Comparison of the changes in diary card variables from baseline to the final 2 weeks of treatment (weeks 11–12) revealed significant differences in favour of group A for all variables. Fig. 1 shows the changes in symptom severity scores. The median daily number of inhalations of rescue bronchodilator decreased slightly, by 0.01 (from 0.5 at baseline), in group A, and increased by 0.72 (from 0.6 at baseline) in group B ($P=0.013$ between

groups). Fig. 2 shows the changes in morning and evening PEF over the 12-week treatment period. The difference between groups for morning PEF was particularly marked.

The patients' overall opinion of treatment efficacy was significantly in favour of group A ($P<0.01$), 83% of patients considering treatment to be very or moderately effective compared with 45% in group B (Fig. 3).

The two groups did not differ significantly in the change in lung function measured at the clinic (PEF, FEV₁, and FVC) from baseline to weeks 11–12 of treatment. Within the groups, a statistically significant ($P=0.032$) decrease in FVC (change from baseline to weeks 11–12 of -0.06 l) in group B was considered clinically unimportant. The physicians' overall opinion of efficacy matched that of the patients, so that, again, treatment was considered very or moderately effective in 83% (group A) and 45% (group B) of cases (Fig. 3).

In group A, eight (26%) patients reported a total of 19 adverse events, compared with nine (28%) patients in group B reporting a total of 17 events.

Table 1. Patient characteristics at entry to study

	Group A SCG + terbutaline	Group B Placebo + terbutaline	All patients
Number (F/M)	30 (11/19)	32 (13/19)	62 (24/38)
Mean age (range), years	10.2 (5–15)	10.3 (6–15)	10.3 (5–15)
Mean duration of asthma (range), years	5.2 (1–12)	6.3 (1–13)	5.8 (1–13)
Mean FEV ₁ (range), % of predicted normal	98.7 (78–149)	98.6 (72–160)	98.6 (72–160)
Type of asthma (extrinsic/intrinsic/mixed), <i>n</i>	25/3/2	29/2/1	54/5/3
Asthma severity, mean score on 0–3 scale*	1.60	1.37	1.48
Steroid at admission (BDP/budesonide), <i>n</i>	13/17	16/16	29/33

* Asthma severity was recorded at first clinic visit on scale of 0–3 where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
SCG: sodium cromoglycate, BDP: beclomethasone dipropionate.

Table 2. Disposition of patients

	Group A SCG + terbutaline	Group B Placebo + terbutaline
Patients randomized to test treatment	31	32
Patients excluded from efficacy analysis	1 (patient withdrew with dizziness after 4 days of treatment)	0
Patients analysed for efficacy	30	32
Patients excluded from safety analysis	0	0
Patients analysed for safety	31	32
Patients withdrawn for worsening asthma	1	11
Time of withdrawal (number of days of treatment) and rate of asthma deterioration		
Days 1–7	0	0
Days 8–14	0	0
Days 15–21	0	0
Days 22–28	0	28 gradual
Days 29–35	0	32 sudden
Days 36–42	0	36 gradual
		41 gradual
Days 43–49	0	43 gradual
Days 50–56	0	54 required inhaled steroid
Days 57–63	62 sudden	57 gradual
		62 gradual
		63 gradual
Days 64–70	0	68 gradual
Days 71–77	0	73 gradual
Days 78–84	0	0

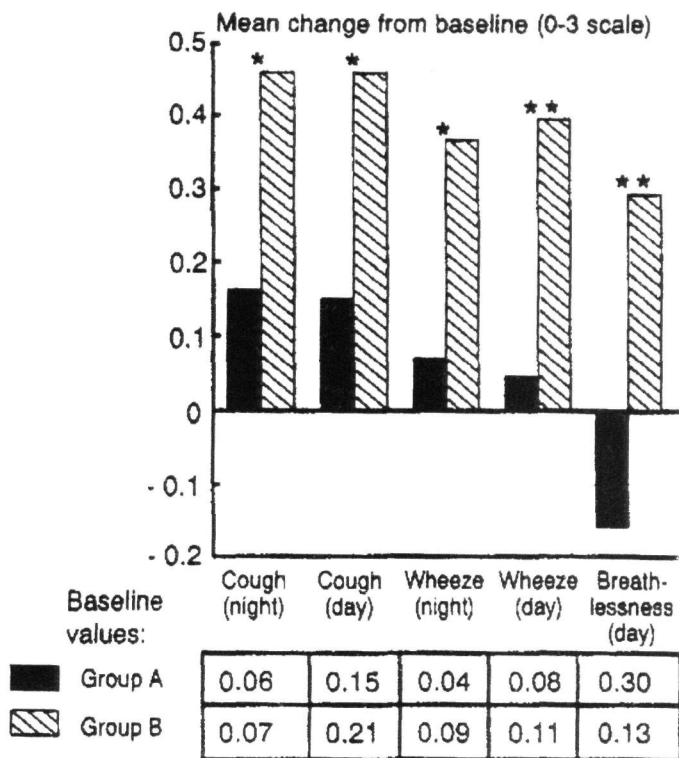


Fig. 1. Change from baseline to weeks 11-12 of treatment in severity of asthma symptoms. Severity scores (0-3 scale) were recorded daily on diary cards and averaged for each 2-week period. Baseline mean values of severity scores for each of symptoms for group A (sodium cromoglycate plus terbutaline) and group B (placebo plus terbutaline) are shown in Table 1. * $P < 0.05$, ** $P < 0.01$ between groups.

The events which were thought to be possibly or probably related to test treatment were abdominal pain and dizziness (all reported by one patient in group A), and asthma, dyspnoea, and hay fever (reported separately by three patients in group B). Apart from the group A patient who withdrew because of dizziness after 4 days of treatment, none of the events resulted in withdrawal.

Discussion

Sodium cromoglycate has been used for asthma for over 20 years. Original investigations of its efficacy and safety were largely carried out in severe asthma, and sodium cromoglycate was found to be both effective and safe (8-10) and to have a useful oral steroid-sparing effect (11, 12). Later studies in children with mild-to-moderate asthma showed that sodium cromoglycate was more effective than terbutaline alone (13), and that its efficacy was comparable with that of an inhaled corticosteroid (14, 15).

In our study, treatment with sodium cromoglycate provided an effective substitute for inhaled corticosteroids, and asthma control was well maintained both during and after withdrawal of the inhaled steroids in this group of children with mild-to-moderately severe asthma. Regular administration of terbutaline was common to both test treatment groups and, as might be expected, was unable on

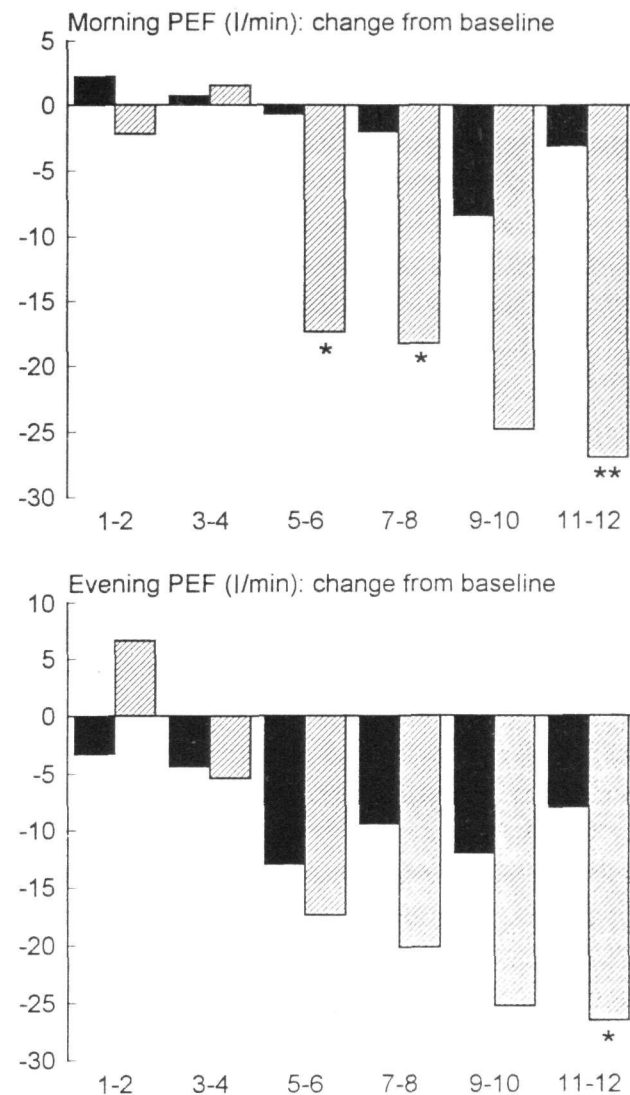


Fig. 2. Morning and evening PEF in treatment groups A (sodium cromoglycate plus terbutaline; solid bars) and B (placebo plus terbutaline; hatched bars). * $P < 0.05$, ** $P < 0.01$ between groups. Each point represents mean of daily diary card measurements over 2-week period.

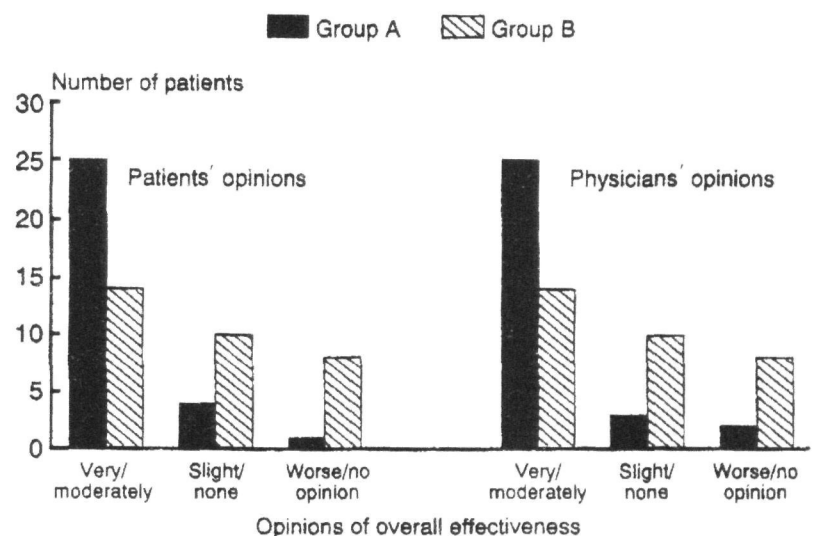


Fig. 3. Patients' and clinicians' opinions of overall effectiveness of test treatment. For both sets of opinions, difference between groups in ratings of "very/moderately effective" was statistically significant ($P = 0.008$).

its own to provide the level of asthma control obtained with regular anti-inflammatory treatment, either inhaled steroids or sodium cromoglycate. The importance of anti-inflammatory treatment in controlling asthma, even in mild asthma, was

demonstrated by the fact that one-third of the patients in the placebo plus terbutaline group were unable to tolerate withdrawal of the inhaled steroids, and a significant increase in asthma symptoms was observed across the group.

The corticosteroids are the most effective agents for the suppression of inflammation. Sodium cromoglycate also has anti-inflammatory effects shown both *in vitro* (16, 17) and in asthmatic patients *in vivo* (18). Laitinen et al. reported no change in indicators of airway inflammation with regular use of terbutaline in adults with newly diagnosed asthma (4). Our results in children with mild asthma confirm previous findings (19) that regular terbutaline alone is an inadequate first-line treatment for asthma and that anti-inflammatory treatment – in this case, sodium cromoglycate – is needed for optimum control of asthma.

In retrospect, it would have been interesting to continue into a third treatment phase in which the regular terbutaline was withdrawn, in order to see whether further improvements could have been obtained by using what is now the recommended standard treatment of mild-to-moderate asthma such as these children had, i.e., a daily inhaled anti-inflammatory drug and symptomatic β_2 -agonists used only as needed (3). Despite reports linking the regular use of certain β_2 -agonists to deterioration in asthma control (20, 21), we felt it prudent to include a regular β_2 -agonist in the present study, since the reduction and withdrawal of inhaled steroid were likely to dispose to asthma exacerbation.

If treatment recommendations are adopted, more patients with asthma at the mild end of the spectrum will be given a daily anti-inflammatory drug and they will probably need to continue with this treatment for many years. For such patients, who are less limited by their disease than those with severe asthma, safety of treatment is of prime importance, and it is because of this that paediatric asthma management guidelines recommend that every child should receive a trial of sodium cromoglycate before resorting to inhaled corticosteroids (3, 7). Recent international guidelines have also suggested that, after inhaled steroids have been added to treatment in children and asthma is controlled, these agents might be tapered off and control maintained with sodium cromoglycate (or nedocromil sodium) alone (3). Our results support this approach to treatment.

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