Long term study of the effect of sodium cromoglycate on non-specific bronchial hyperresponsiveness

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ABSTRACT A double blind, crossover study was undertaken to determine whether non-specific hyperresponsiveness in subjects with asthma was reduced by long term treatment with sodium cromoglycate and, if so, whether this was related to change in lung function. Forty four adult asthmatic subjects (41 atopic, three non-atopic) entered the one year study at intervals staggered over six months. After a baseline period to ensure that asthma control was stable subjects entered the treatment period, during which they inhaled sodium cromoglycate 20 mg four times daily or matching placebo four times daily for 16 weeks each, in random order. Response was assessed at four weekly intervals by measurement of lung function and histamine inhalation tests, from which the provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀H) was calculated. The assessment included daily symptom score, morning and evening Airflometer readings and treatment; mean values for each treatment period and also for the final four weeks of each period were compared. There were no significant differences between placebo and sodium cromoglycate treatment for PC₂₀H, FEV₁, morning or evening flow meter readings, bronchodilator usage, or symptom scores for the group as a whole, for the 16 week period or for the final four weeks of each period. Thirteen subjects showed better morning and evening flow meter readings while taking sodium cromoglycate than while taking placebo and eight better readings with placebo than with sodium cromoglycate (p < 0-05). Improvement in lung function did not correlate with baseline lung function or baseline PC₂₀H, or with features of atopy. These results suggest that long term sodium cromoglycate treatment does not alter non-specific bronchial responsiveness in adult asthmatic subjects.

Many drugs used for the symptomatic treatment of asthma have been shown in short term or single dose studies to modify both specific and non-specific airway hyperresponsiveness.¹⁻⁴ This effect is seen acutely with β₂ adrenoceptor agonists,⁵⁻⁷, which nevertheless have not been shown to reduce airway responsiveness to histamine over a four week period.⁴⁻⁷ Two non-bronchodilator agents, inhaled sodium cromoglycate⁸⁻¹¹ and inhaled corticosteroids,¹² have been reported to reduce non-specific airway hyperresponsiveness over longer periods of time. When the present study began no double blind, placebo controlled study examining the long term effect of sodium cromoglycate on airway hyperresponsiveness had been performed. While some circumstantial evidence, combined with a theoretical understanding of the drug's mode of action,¹³⁻¹⁵ suggested that sodium cromoglycate could reduce non-specific hyperresponsiveness, most of the data supported this hypothesis only indirectly.⁸⁻⁹¹⁶⁻¹⁸ Most single and multiple dose studies of the effect of sodium cromoglycate on histamine hyperresponsiveness have not shown any appreciable protection.¹⁹⁻²¹ Two more recent double blind, placebo controlled studies¹⁰⁻²² failed to find a significant change in bronchial responsiveness to methacholine or histamine after treatment with sodium cromoglycate for two weeks.

Our study was undertaken to examine the hypothesis that long term administration of sodium cromoglycate could reduce non-specific bronchial hyperresponsiveness in subjects with chronic asthma. The relationship between change in airway obstruction and change in responsiveness was also examined to determine whether any observed effect was dependent on change in lung function.

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Methods

SUBJECTS

Forty eight subjects with asthma (as defined by the American Thoracic Society) entered the study. Twenty were male and 28 female, their ages ranging from 15 to 65 (mean 37 years). Twenty patients had first developed asthma before they were 10, and 11 at the age of 40 or more. All were non-smokers, although eight had smoked previously. Mean FEV₁ was 2-271 (72% predicted, range 37–103% predicted). The geometric mean PC₂₀₇ was 0-37 (range 0-05–5-66) mg/ml. Most subjects had moderate asthma with symptoms requiring more than one form of treatment for control. Further clinical and lung function details are given in table 1.

STUDY DESIGN

The study was of double blind, randomised, placebo controlled crossover design. Subjects entered the trial at intervals staggered over six months, beginning in March, and the trial lasted one year for each subject. This year was divided into a baseline period (8 weeks), two treatment periods (each 16 weeks) and a washout period (12 weeks). Visits were made to the respiratory laboratory for review by the investigator and for lung function tests at 0, 4, 8, 14, 20, 24, 30, 36, 40, 46, and 52 weeks, as shown below.

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>14</th>
<th>20</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>40</th>
<th>46</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>Washout</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Active or placebo</td>
<td></td>
<td></td>
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<tr>
<td>Placebo or active</td>
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</tbody>
</table>

At the first visit a modified Brompton Hospital respiratory questionnaire was administered and skinprick testing with 26 common allergens performed. Blood was taken for a full blood count, determination of serum IgE levels, and testing for Aspergillus precipitins. Patients were instructed in the use of the diary card and taught to use the Airflometer, a portable instrument used for monitoring lung function at home. The readings (in AFM units), have been shown to reflect both expiratory flow rate and total expired volume (FVC). At this visit patients also gave informed written consent to the protocol, which had been approved by the hospital ethics committee. Lung function studies and a histamine inhalation test (HIT) were performed at this and all subsequent visits to the laboratory. At subsequent visits diary cards were reviewed and collected, and a diary card was issued for the next four weeks.

At week 8 patients were issued with their trial treatment for the following 16 weeks (treatment 1). Subjects were randomly assigned to receive active drug or placebo during treatment period 1 and were issued with eight canisters, each with two weeks' supply of capsules. They were instructed to inhale one capsule from a Spinhaler (Fisons) four times daily. The active and placebo capsules were identical in appearance, although the active drug (sodium cromoglycate 20 mg plus lactose 20 mg—Spincaps, Fisons) and placebo (lactose 20 mg) differed slightly in taste. At week 24 all unused treatment was returned and patients were issued with a new box of capsules (treatment 2) and a new Spinhaler.

While some rationalisation of the treatment took place during the baseline period, prescribed asthma treatment was not altered subsequently unless uncontrolled symptoms of asthma necessitated the addition of oral corticosteroids. This occurred in seven subjects. Patients were encouraged to reduce or increase their use of inhaled β₂ agonists if their symptoms warranted it and instructed to note all details of change in treatment in the diary card.

LUNG FUNCTION AND HISTAMINE INHALATION TESTS

All lung function tests were performed in an air conditioned laboratory, at the same time of day for each subject. Lung volume measurements, by helium dilution (Collins lung volume module), included vital capacity (VC), functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC). Spirometry was performed with a water sealed Godart spirometer. Patients were instructed not to take inhaled β₂ agonists, beclomethasone dipropionate, or sodium cromoglycate for six hours, or theophylline for 24 hours, before each appointment.

The histamine inhalation test was performed with a Rosenthal-French Dosimeter and de Vilbiss nebuliser (No 646) according to the method of Chai et al and the dose response curve was constructed according to the method of Cockcroft et al. Briefly, aerosol was inhaled at five minute intervals by taking five breaths from the nebuliser, beginning with phosphate buffered saline (control) and followed by phosphate buffered histamine administered in doubling incre-

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Table 1 Clinical details of 48 subjects with asthma

<table>
<thead>
<tr>
<th>Sex (M:F)</th>
<th>20:28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y): mean (SD)</td>
<td>36-5 (16-1)</td>
</tr>
<tr>
<td>Age (y) at onset: mean (SD)</td>
<td>19-1 (18-8)</td>
</tr>
<tr>
<td>Number with positive SPT</td>
<td>41</td>
</tr>
<tr>
<td>FEV₁ (% pred): mean (SD)</td>
<td>71-9 (18-6)</td>
</tr>
<tr>
<td>PC₂₀₇ (mg/ml): mean</td>
<td>0-37</td>
</tr>
<tr>
<td>FEV₁ (l): mean (SD)</td>
<td>2-27 (0-80)</td>
</tr>
</tbody>
</table>

No of patients having baseline treatment with:
- salbutamol only 9
- salbutamol and beclomethasone 17
- salbutamol, beclomethasione, theophylline 19
- salbutamol and theophylline 3

SPT—skinprick test reactions (positive if > 2 mm weal in response to one or more of 26 common allergens); FEV₁—forced expiratory volume in one second; PC₂₀₇—provocative concentration of histamine causing a 20% fall in FEV₁.
ments from 0.03 mg/ml to a maximum of 16 mg/ml. Response was measured by change in forced expiratory volume in one second (FEV₁) at 30 and 90 seconds after the last inhalation, and the test was stopped when the FEV₁ fell by 20% or more from the lowest post saline value. The dose-response curve was constructed and the result expressed (in mg/ml) as the provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀H).

DIARY CARDS
Each patient kept a daily record of symptoms, treatment, and morning and evening Airflometer readings, for which careful instruction and supervision were given. Patients recorded the best of three readings, morning and evening, taken before bronchodilator. Symptoms (day and night asthma, cough, and sputum) were graded in severity from 1 to 4 (none to severe), and all treatment, including the number of trial capsules taken, was recorded daily.

STATISTICAL ANALYSIS
To compare treatment responses to sodium cromoglycate and to placebo, the data for all 40 subjects were pooled for analysis, and the Student’s paired t test and Wilcoxon rank sum analysis were used. Values for all lung function and histamine inhalation test measurements were taken from each visit and the mean for each treatment period was compared. In addition, the last four weeks of each treatment period were compared. Mean weekly values from the diary card (symptom score, morning and evening flow meter readings, and treatment usage) were calculated. The mean value for all 16 weeks and for the last four weeks were compared for each treatment period. Paired t tests were also used to test for a treatment effect between the groups receiving sodium cromoglycate and placebo as initial treatment. All PC₂₀H values were logarithmically transformed. Change in PC₂₀H was assessed by comparing the PC₂₀H fold change (PC₂₀H after treatment: PC₂₀H before treatment) before and at the end of each treatment period. Subgroup analysis (t tests) were also performed to compare pollen sensitive subjects receiving sodium cromoglycate with those receiving placebo in the spring, and also subjects treated with sodium cromoglycate in Spring with those treated later in the year, in an attempt to determine whether seasonal factors were important.

Results
Forty eight patients with asthma were admitted to the study and 40 were able to complete it. Three subjects dropped out during the baseline period (one through unrelated illness, two because of inability to attend the laboratory) and a further five subjects (three having placebo and two sodium cromoglycate) at the end of treatment 1 (one having cromoglycate, because of moderately severe asthma requiring frequent courses of oral corticosteroids and admission to hospital, and two due to inability to continue attending the laboratory).

Although subjects were randomly allocated to receive placebo or sodium cromoglycate first the resulting groups differed (p < 0.05) with respect to age at entry into the study (mean 33 (SEM 3) years for cromoglycate v 45 (3) years for placebo) and age of onset of asthma (14 (4) (3) years for cromoglycate v 25 (5) years for placebo). None of the other clinical and lung function indices differed significantly between the two groups.

For the group as a whole there was no significant difference between placebo and active treatment periods for lung function or symptoms (FEV₁, morning and evening flow meter readings, symptom score, lung volumes) or for PC₂₀H values (see tables 2 and 3). This was true both for the total treatment period and for the last four weeks of each period, and was also true when non-parametric analysis was used. Significantly fewer subjects took prednisone during the cromoglycate period than during the placebo period (3 v 7) but no other measure of response (lung function, β₂ agonist use, or symptom score) differed

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>SCG</th>
<th>Placebo</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁(1) (l)</td>
<td>2.3 (SD 0.7)</td>
<td>2.3 (SD 0.7)</td>
<td>2.3 (SD 0.8)</td>
<td>2.2 (SD 0.8)</td>
</tr>
<tr>
<td>FEV₁%P</td>
<td>72.8 (SD 16.3)</td>
<td>73.4 (SD 14.5)</td>
<td>72.3 (SD 16.5)</td>
<td>69.0 (SD 16.7)</td>
</tr>
<tr>
<td>PC₂₀H (mg/ml)</td>
<td>0.44 (0.06–3.4)</td>
<td>0.62 (0.12–3.18)</td>
<td>0.66 (0.09–4.8)</td>
<td>0.65 (0.09–4.7)</td>
</tr>
<tr>
<td>PC₂₀H (mg/ml) excluding URTI</td>
<td>0.44 (0.06–4.7)</td>
<td>0.60 (0.17–3.10)</td>
<td>0.66 (0.10–4.5)</td>
<td>0.65 (0.04–4.7)</td>
</tr>
<tr>
<td>PC₂₀H (mg/ml) SCG first</td>
<td>0.49 (0.08–1.95)</td>
<td>0.64 (0.16–2.47)</td>
<td>0.49 (0.07–3.5)</td>
<td>0.62 (0.09–4.35)</td>
</tr>
<tr>
<td>PC₂₀H placebo first</td>
<td>0.52 (0.04–6.5)</td>
<td>0.63 (0.09–4.48)</td>
<td>0.98 (0.16–5.94)</td>
<td>0.71 (0.09–5.68)</td>
</tr>
<tr>
<td>PC₂₀H (mg/ml) whole group, last 4 weeks</td>
<td>0.54 (0.04–6.7)</td>
<td>0.58 (0.07–5.1)</td>
<td>0.50 (0.04–6.1)</td>
<td>0.62 (0.13–2.9)</td>
</tr>
<tr>
<td>PC₂₀H (mg/ml) last 4 weeks, excluding URTI</td>
<td>0.50 (0.04–6.1)</td>
<td>0.62 (0.06–6.1)</td>
<td>0.62 (0.06–6.1)</td>
<td>0.59 (0.02–13.6)</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in one second; PC₂₀H, provocative concentration of histamine causing a 20% fall in FEV₁; SCG, sodium cromoglycate; %P, value expressed as a % of the predicted normal for sex, age, and height; URTI, upper respiratory tract infection.
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Table 3 Group mean values (with standard deviations in parentheses) for the four study periods: diary card

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>SCG</th>
<th>Placebo</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>39.46 (8.09)</td>
<td>35.81 (8.42)</td>
<td>35.69 (7.23)</td>
<td>36.53 (9.30)</td>
</tr>
<tr>
<td>Morning AFM</td>
<td>56.49 (37.72)</td>
<td>63.43 (43.09)</td>
<td>68.81 (43.27)</td>
<td>62.22 (44.05)</td>
</tr>
<tr>
<td>Evening AFM</td>
<td>65.43 (39.12)</td>
<td>72.18 (44.48)</td>
<td>75.09 (43.13)</td>
<td>69.87 (43.39)</td>
</tr>
<tr>
<td>Inhaled bronchodilator (puffs/week)</td>
<td>57.39 (28.0)</td>
<td>57.30 (29.88)</td>
<td>54.93 (30.54)</td>
<td>60.60 (29.70)</td>
</tr>
<tr>
<td>Oral corticosteroids (mg/week)</td>
<td>18.70 (13.69)</td>
<td>6.68 (2.71)</td>
<td>33.08 (36.37)</td>
<td>14.92 (7.90)</td>
</tr>
<tr>
<td>Inhaled corticosteroids (puffs/week)</td>
<td>62.53 (26.53)</td>
<td>57.94 (26.89)</td>
<td>62.93 (27.35)</td>
<td>66.34 (25.70)</td>
</tr>
<tr>
<td>Theophylline (mg/week)</td>
<td>351.4 (177.0)</td>
<td>368.0 (179.3)</td>
<td>409.44 (166.8)</td>
<td>388.97 (182.7)</td>
</tr>
</tbody>
</table>

*7 subjects 13 subjects 26 subjects
AFM—airflow meter readings; SCG—sodium cromoglycate.

significantly between cromoglycate and placebo periods either for the whole period or for the last four weeks of each period.

Forty one episodes of upper respiratory tract infections occurred in 33 subjects during the year. Nine of these occurred outside either treatment period and 12 were during sodium cromoglycate and 10 during placebo treatment. When all PC_{20}H values recorded within six weeks of an upper respiratory tract infection were excluded, there was no difference between cromoglycate and placebo PC_{20}H values for the whole period or for the last four weeks only. When the PC_{20}H data on pollen sensitive subjects treated in spring were analysed separately the mean fold change in PC_{20}H over the months August-November (peak pollen count) did not differ significantly between subjects taking sodium cromoglycate (1.4) and those taking placebo (1.9).

Individual changes in lung function were assessed by comparing t score differences for each subject between active and placebo treatment periods. Thirteen subjects showed a significant (p < 0.05) improvement in morning and evening AFM while taking sodium cromoglycate, the mean morning flow meter reading being 66 (SD 53) for cromoglycate and 57 (44) for placebo. The mean FEV_{1} % predicted for these subjects was 71 (16) for cromoglycate and 64 (17) for placebo. The mean PD_{20}H did not, however, differ significantly between cromoglycate and placebo periods, the mean values with 95% confidence limits being 0.67 (0.07-6.6) and 0.62 (0.06-6.1) mg/ml respectively. Eight subjects had significantly better morning and evening flow meter readings during placebo than during cromoglycate periods. Several clinical indices were used to examine the possible differences between responders to cromoglycate and non-responders (table 4). The only significant difference was in age of onset of asthma, which was 15 (SD 4) years for responders and 24 (4) years non-responders (p < 0.01).

Discussion

The findings of this study suggest that the administration of sodium cromoglycate to adults with asthma does not alter non-specific bronchial hyperresponsiveness during 16 weeks, a period in which therapeutic benefit could be expected to be seen. Improvement in lung function occurred in 13 of the 48 subjects, but even this group showed no difference in PC_{20}H values between cromoglycate and placebo periods. The results concur with those of studies conducted over shorter periods, which have shown attenuation of the airway response to specific stimuli, such as allergen and cold air, but not to histamine or methacholine. \(^{10, 20, 27}\)

The well established efficacy of sodium cromoglycate in the context of specific bronchial provocations, such as exercise, \(^{28}\) allergen, \(^{11, 19}\) and cold air, \(^{27}\) along with its usefulness as a prophylactic agent in asthma, \(^{1, 11, 17, 18}\) has led to the speculation that it may reduce non-specific bronchial hyperresponsiveness. Data suggesting that long term administration of cromoglycate could reduce non-specific bronchial hyperresponsiveness first came from Altounyan in 1970, \(^{8}\) who documented a reduction in histamine responsiveness after two weeks' treatment
with the drug in one individual during the pollen season. Subsequently, Altounyan documented a similar reduction in histamine responsiveness in 10 subjects during the pollen season, despite no change in baseline FEV₁. This effect probably results from prevention of the allergic reaction during the pollen season, which thus inhibits an allergen induced increase in non-specific bronchial responsiveness.

Dickson has reported a one year trial of a combination of sodium cromoglycate and isoprenaline in 24 asthmatic children. The percentage fall in FEV₁ in response to a single dose of histamine was less while they were taking sodium cromoglycate-isoprenaline than three to seven days after withdrawal. The study was neither blind nor placebo controlled, however, and possibly the β₂ agonist was contributing to this effect. Silverman could not detect any change in histamine responsiveness in a year long, placebo controlled and double blind, parallel study of cromoglycate-isoprenaline compound in 53 asthmatic children. Of four more recent studies examining the effect of cromoglyc on non-specific responsiveness, three have not shown any benefit, while one found an increase in PC₂₀H over six weeks, though the magnitude of the change was not stated. The weight of evidence therefore indicates a role for cromoglycate in preventing the consequences of natural allergen exposure and of modifying the airway response to specific stimuli such as exercise and cold air, but does not confirm a direct effect in reducing non-specific responsiveness.

For the subgroup whose lung function improved with sodium cromoglycate there was no association between an improvement in lung function and a reduction in non-specific responsiveness as measured by PC₂₀H. There was no difference in mean PC₂₀H values between those who improved in lung function and those who did not, suggesting that baseline non-specific responsiveness is not a determinant of the therapeutic response to cromoglycate.

Although the results from this study concur with those from several single dose and short term studies, other possible reasons for a lack of change in PC₂₀H should be considered. Firstly, while PC₂₀H is highly reproducible over short periods, it is probably less reproducible over weeks and months. Detecting a significant change in non-specific responsiveness is therefore more difficult in studies of several months than in short term studies. In addition, using a drug that does not usually benefit all patients introduces the problem of a varying response, militating against a statistically significant change in PC₂₀H for the whole group.

One of the aims of the staggered entry into the study over a six month period was to dilute any seasonal effect. More pollen sensitive subjects took sodium cromoglycate than placebo in spring by chance. The change in PC₂₀H for this subgroup was no different from that of the pollen sensitive subjects taking placebo in spring, so allergen exposure seems an unlikely explanation for a lack of improvement in non-specific responsiveness in these subjects. Very few subjects were sensitive only to pollen, and for most common inhaled allergens exposure is year round in Sydney.

Ideally, to examine the effect of sodium cromoglycate on non-specific responsiveness, subjects having minimal asthma treatment would be most suitable, minimising treatment interaction as well as the fluctuations in lung function that occur in more severely affected subjects. Beclomethasone has been reported to reduce non-specific responsiveness, and may reduce the potential therefore for a further increase in PC₂₀H; but there was no significant difference between change in PC₂₀H in subjects taking beclomethasone and those who were not. Possibly the administration of oral corticosteroids to seven subjects during the placebo period prevented a fall in PC₂₀ that would have resulted in a significant difference between mean PC₂₀H values for the cromoglycate and placebo periods. Omission of the data for these subjects, however, does not result in a different outcome for PC₂₀H change. Indeed, oral corticosteroids may not result in an improvement in non-specific airway reactivity except at very high doses. Finally, fluctuations in baseline lung function could possibly have contributed to the lack of change in PC₂₀H during active treatment; but analysis of PC₂₀H values after exclusion of all subjects with a greater than 10% variability in baseline FEV₁ did not alter the outcome of the study. Several studies have documented a change in PC₂₀H despite stable lung function. Although the level of airways obstruction has a significant but in most studies weak relationship to non-specific responsiveness, it is probably not the major determinant of such responsiveness in asthma.

The results of the study show that the administration of sodium cromoglycate to subjects with chronic, stable asthma did not alter non-specific responsiveness to histamine during 16 weeks. PC₂₀H did not change in subjects whose lung function improved significantly.

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