Sodium cromoglicate: an ineffective drug or meta-analysis misused?

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Sodium cromoglicate (SCG) has been available since around 1970 for the treatment of asthma and other allergic disorders in both adults and children. It has been approved for use around the world. Over the period of its development, a number of different formulations were introduced. In 1999, a systematic review of SCG use in childhood asthma was carried out and reported initially as a poster. Further systematic reviews and papers followed from the same authors and finally a Cochrane Collaboration review was published in 2003. All concluded that SCG was ineffective in paediatric asthma. Both the British Thoracic Society Guidelines for the treatment of paediatric asthma and the Model List of Essential Drugs of the WHO now reflect these conclusions. This paper looks carefully at the conclusions of these systematic reviews and raises concerns about the interpretation of the results. These failed to take adequate account of the changes with time in both the formulations used and the age groups examined, and also failed to take adequate note of the totality of information available over all end-points. One primary end-point was based on only four out of the 24 studies included in the review. Rather than having no effect, it is demonstrated that a considerable body of evidence favours SCG compared to placebo and, far from being ineffective, the drug appears to be effective particularly in older children. This article replaces a previously published version. DOI: 10.1002/pst.258. Copyright © 2007 John Wiley & Sons, Ltd.

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INTRODUCTION

Sodium cromoglicate (SCG) was discovered in 1965 by the late Dr. Roger Altounyan and developed by Fisons Pharmaceuticals for use as an inhaled drug in asthma, primarily of allergic origin [1]. The drug was selected after over 200
compounds had been tested by Altounyan as it provided greater than 50% protection for up to 6 h against bronchial allergen challenge in a human subject, himself. The first inhaled product to be developed, Intal Compound, was a capsule containing 20 mg SCG powder mixed with 20 mg lactose powder and 0.1 mg isoprenaline, a short-acting bronchodilator. The powder was inhaled from the capsule using an inhalation device, the Spinhaler. The addition of the isoprenaline was considered necessary, to prevent the bronchoconstriction that can occur in some asthmatic patients following the inhalation of a sodium salt. In order to provide 24 h protection against inhaled bronchial allergen, the recommended dosage schedule was 20 mg four times daily.

The first clinical trials were carried out in adults and compared Intal Compound capsules with capsules containing 0.1 mg isoprenaline mixed with lactose. The first controlled trial [2] was conducted in patients with severe, steroid-dependent asthma and used a double-blind, cross-over sequential design. The end-point was the clinician’s assessment at the end of the two treatment periods as to which treatment period had been better or whether there was no difference. The first analysis was carried out after 10 patients had completed the trial. It was found that all preferences were in favour of Intal Compound. Further trials in adult patients followed; these compared Intal Compound with isoprenaline + lactose. Most were of short duration, to a double-blind cross-over design. The outcome measures used were the change in asthma symptom scores recorded by patients on daily diary cards, the clinicians’ assessment of asthma severity at clinic visits, the use of rescue bronchodilators, the reduction in the dose of oral steroids and lung function tests, either recorded daily by the patient or measured at clinic visits. In the first four trials published [3–6], results of 34 outcome measures were reported; all were in favour of SCG, none in favour of placebo. Of these outcome measures, 23 were statistically significant in favour of SCG and 11 were not.

In the early days of development, some authorities questioned the role of the isoprenaline and a product without isoprenaline, Intal Plain, was produced. The first long-term trial compared, Intal Compound, Intal Plain, isoprenaline and placebo (lactose powder). This trial was designed, conducted and analysed by the Medical Research Council in the UK [7]. The trial was a double-blind, group comparative design in 103 adult patients with asthma symptoms sufficient to interfere with their normal lives and not controlled by a pre-treatment standard panel of drugs. The outcome measure was the proportion of patients at the end of 12 months treatment, whose asthma was controlled satisfactorily in the judgement of the clinician and had not been withdrawn because of inadequate asthma control. At the end of the first year, the proportions of patients remaining well on, Intal Compound, Intal Plain, isoprenaline and placebo were 80%, 67%, 25% and 16%, respectively.

The first trial in children compared Intal Compound with isoprenaline in 51 children aged 5–16 years [8]. The trial was a double-blind, cross-over design, each treatment period being 4 weeks. Patients or parents kept daily diary cards recording asthma severity, day and night, cough, sputum and use of rescue bronchodilators. Overall patient assessments were carried out at the end of each treatment period, lung function tests were performed every week and the change in oral corticosteroid requirements was recorded. Again the initial analysis used a sequential approach carried out by an independent assessor who examined all the records. Altogether 18 cases were required to reach a statistically significant result in favour of Intal Compound. Eleven of these cases were thought by the assessor to have improved during the Intal Compound period, one during the isoprenaline period and in five cases there was no significant change in either period. One case had been withdrawn and the code broken. Statistical tests were not reported on all outcome measures. Preference for active treatment was statistically significant as recorded by both the clinician \((p<0.005)\) and the patient \((p<0.005)\). Statistical tests were reported on the outcome of lung function tests; all (10) were in favour of Intal Compound, and eight were statistically significant in favour of Intal Compound.
The first long-term trial in children compared Intal Compound and isoprenaline in 53 asthmatic children of mean age 8 years [9]. The treatment period was 12 months and the end-point similar to the long-term adult trial, the proportion of patients who remained well. At the end of 12 months, 71% of patients treated with Intal Compound remained well compared to 24% treated with isoprenaline.

There have been no comparative trials of Intal Compound and Intal Plain in childhood asthma. The first trials with Intal Plain in children were carried out in the USA.

Intal Compound and Intal Plain were approved for use in asthma in many countries throughout the world, including the UK and Europe. Some countries, including the USA and Japan, only approved Intal Plain and did not accept Intal Compound as they considered it necessary to demonstrate that the combination was ‘better’ than either component administered separately. The outcome of most comparative trials between Intal Compound and Intal Plain favoured Intal Compound, although the differences did not achieve statistical significance.

The drug became an accepted clinical tool in the treatment of both seasonal and perennial allergic asthma. Over subsequent years, new formulations were developed for other indications and the indications were expanded to include seasonal and perennial allergic rhinitis, allergic conjunctivitis, inflammatory bowel disease, food allergy and systemic mastocytosis.

In asthma, the Spinhaler was considered to be a complex and difficult method of administration which could not be used by children under the age of 5 years, and alternative formulations were developed. The first of these was an aqueous solution to be administered by a powered nebulizer for the treatment of children under 5 years of age and infants. With improved delivery technology, pressurized, metered dose aerosols were developed, the first delivering 1 mg/puff and a later one delivering 5 mg/puff. In order to improve the coordination using metered dose inhalers (MDI), and to improve the dose delivered and the distribution of the dose within the lungs, devices have been added or recommended for use, particularly in children. These have included a 10 cm open tube extension, the Syncroner, and a 750 ml spacer/holding chamber, the Fisonair. However, other spacers of different volume sizes are available and these have been used in some trials. Each of these delivery systems will deliver a different dose to the lung and a different distribution within the lung. As it has been shown [10] that the efficacy in providing protection against inhaled allergen, the primary mode of action, is dependent upon both the dose delivered to the lung and the evenness of distribution of the drug within the bronchial tree, the delivery system used will be a critical factor in achieving clinical efficacy.

Intal Compound and Intal Plain were first introduced into clinical usage in 1969. The aqueous nebulizer solution was introduced in the early 1970s, the 1 mg MDI in the late 1970s and the 5 mg MDI in the early 1980s.

SCG was the first of a new drug class (chromones) to be introduced into clinical medicine for many years. Since its introduction, many pharmaceutical companies have been involved in asthma research and a number of drugs have been developed with differing postulated modes of action. Despite these advances, the management of asthma remains a problem. It is therefore important that physicians continue to have the widest range of tools in their armamentarium for the treatment of asthma symptoms.

In recent years meta-analyses and systematic reviews have been increasingly used to bring information together on the effect of drug interventions, whether this be the effect relative to placebo or the effect relative to other available products, to help guide the use of such interventions. This methodology has been aided by the availability of tools through the Cochrane Collaboration. In many cases the Collaboration has been instrumental in facilitating such reviews to provide guidance on the estimated size of effect of the respective interventions and indeed whether such interventions have any demonstrated effect at all. However, meta-analyses and systematic reviews need to be carried out with great care. They can be complicated and their conclusions

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may have wide-ranging consequences. It is therefore important to ensure that the methodology and the conclusions are correct.

SYSTEMATIC REVIEWS OF INHALED SODIUM CROMOGLICATE IN CHILDHOOD ASTHMA

Over the last few years the use of SCG in childhood asthma has been the subject of several related systematic reviews and these have in turn been reflected in the prescribing guidelines. The reviews appeared in several published sources:


The First Poster was a systematic review that used a similar approach to the Thorax Paper; the Second Poster used a similar approach to the Cochrane Review. The contents and conclusions of the posters will be discussed briefly, with more detailed critiques of the Thorax Paper and the Cochrane Review. The four presentations came from the same group of authors, albeit in a different order and with an additional author for 3 and 4.

The First Poster

The first information regarding a systematic review of inhaled SCG in children with asthma was presented as a poster at the American Thoracic Society in 1999 [11].

A total of 22 randomized controlled trials were included in the review and results from two symptoms of asthma, namely wheeze and cough, were presented. The results were summarized and indicated that the null hypothesis for homogeneity of treatment effect across studies should be rejected. Under the assumption of heterogeneity, the 95% confidence intervals for the differences between treatments were (0.08, 0.22) for wheeze and (0.12, 0.24) for cough. Additionally, it was stated that the ‘tolerance interval’ included zero and interestingly, that older studies concluded more often in favour of SCG. There was some indication from the funnel plots for publication bias.

Since the 95% confidence interval for the difference between SCG and placebo for both symptoms did not include zero, there appeared to be good statistical evidence to support the conclusion that SCG did have a beneficial effect on these symptoms. The conclusion therefore appears to be based on the ‘tolerance interval’ since the abstract stated that: ‘The overall tolerance interval included zero, thus it cannot be concluded that sodium cromoglycate is superior to placebo.’ Although the results claimed that 22 studies had been identified only 20 were listed in the outcome measures.

The conclusion reached was ‘There is no evidence for a beneficial effect of sodium cromoglycate in children with asthma.’

The Thorax Paper

Following the First Poster, a more detailed description of the systematic review was published in Thorax in 2000 [12].

The systematic review was carried out in a structured way, following literature searches of Medline, Embase, Cochrane Controlled Trial Register with further information obtained from pharmaceutical companies and references from relevant articles. The criteria for inclusion in the review were ‘double-blind placebo-controlled randomized clinical trials of maintenance treatment of children aged 0–18 years published in English’ between January 1966 and January 1999. The studies were assessed for methodological quality, pooled estimates of treatment differences obtained and tested for homogeneity, and funnel plots used to assess for any possible publication bias.

The approach was similar to that carried out in the First Poster. Additional trials were identified and a total of 24 randomized controlled trials were
included, compared with the 20 studies used in the First Poster. In the paper, results for wheeze and cough were presented, the scales for each were transformed to a 0–3 scale. The null hypothesis for homogeneity of treatment effect across studies was rejected and under the assumption of heterogeneity, the 95% confidence intervals for the differences between treatments were (0.11, 0.26) for wheeze and (0.13, 0.27) for cough. The authors further stated that the ‘tolerance interval’ included zero and that older studies were more often in favour of SCG. There was some indication from the funnel plots for publication bias.

The conclusion reached was ‘There is insufficient evidence that SCG has a beneficial effect as maintenance treatment in children with asthma.’

The conclusion was again somewhat surprising based on the data presented and the fact that the authors of the individual papers concluded a positive outcome in favour of SCG in 16 of the studies, a partially positive outcome in three studies, an equal outcome in five studies and no studies in favour of placebo. Since the 95% confidence interval for the difference between SCG and placebo for both symptoms did not include zero, there appeared to be statistical evidence to support the conclusion that SCG did have a beneficial effect on these symptoms. Their conclusion appeared to be based on ‘the apparent publication bias, the small overall treatment effect and the tolerance interval including zero.’ The tolerance intervals were quoted as (−0.11, 0.48) for wheeze and (−0.04, 0.43) for cough. While these do indicate that not ALL future studies will be numerically in favour of SCG, they also indicate that a large proportion (approx. 90%) will be. The authors go on to discuss the heterogeneity of treatment effect across studies and highlight as above the relationship between effect of SCG and date of publication, indicating that this is also a function of age of child, although they do not comment on any potential effect of formulation of SCG or the difficulties of diagnosis in younger children.

It was interesting to note that older studies concluded more in favour of SCG and this further highlights the difficulties in the interpretation of systematic reviews. The trials included were published during the period January 1968 to January 1999 and over such a period there may be important changes occurring in study designs and target populations. For example, over the period 1968–1980, 14 studies were published, 12 used 20 mg dry powder delivered via a Spinhaler (in children age range 5–17 years) and two used 20 mg as nebulizer solution (age range 2–6 years). In all of these studies the diagnosis was asthma. Thirteen of these studies were considered to be positive and one, positive/equal. In contrast, the remaining 10 studies published between 1980 and 1997 used different inhalation systems (nebulizer and MDI), dosage schedules and in some cases a different diagnosis (asthma, wheezy bronchitis, persistent/recurrent wheezing, pre-term babies with respiratory symptoms) and were carried out in children aged 0–6 years (many under one year of age); three of these were considered to be positive, two positive/equal and five equal. This detailed examination of the sequencing of trials does show that the trials demonstrating the efficacy of the drug in childhood asthma were conducted in children over 5 years of age with the drug delivered as dry powder using the Spinhaler and published prior to 1980. The trials published after 1980 were conducted mainly in children aged less than 5 years using either nebulized solution or metered dose aerosol. Thus, ‘older’ trials are confounded with both age of child, formulation of SCG and diagnosis. The nebulizer solution was introduced primarily for the treatment of children under the age of 5 years and it is now known that many children with recurrent wheezing in this age group have a self-limiting condition and do not develop asthma. It is not surprising therefore that in these later trials, it proved more difficult to demonstrate consistently the effect of SCG. All of the 12 trials in older children using the dry powder administered via the Spinhaler showed a statistically significant benefit compared to placebo.

The strength of any systematic review lies in the inclusion of all studies and despite the best efforts made by the authors, we identified a further three large published randomized, placebo-controlled studies [15–17] which were available at the time
of the review. All three showed a statistically significant benefit in favour of SCG and enrolled a total of almost 600 patients (compared to approximately 900 patients in the studies included in the review). Two of these [15,16] were used in major registration dossiers.

The additional information provided in the paper highlights issues that need to be considered in meta-analyses. Firstly, the inclusion of all suitable trials and here we know of at least three placebo-controlled trials all in favour of SCG which are not included and at least two included studies that were not strictly placebo-controlled (comparison was against isoprenaline) and should have been excluded according to the criteria. Secondly, how to handle data on different scales and transform to a common scale – in these summaries both wheeze and cough are presented as separate symptoms but in 12 studies only daytime symptoms were recorded and are used both for cough and wheeze, clearly cough and wheeze assessments here cannot be considered as two assessments. Thirdly, the need to be alert for any confounding factors: Figure 1 shows the mean difference in cough scores by study together with 95% confidence intervals and clearly shows the effect with date of publication and how this is confounded with both formulation and age range of children enrolled. Figure 2 shows the pooled effect of cough symptoms for pre-school and school children, confirming the greater effect in the older children (mostly using the dry powder).

The presentation of tolerance interval is unusual in the context of clinical trials. The usual approach

Figure 1. Difference (SCG-placebo) with 95% confidence intervals for cough symptoms (from Tasche et al. [12]).
is to form a pooled estimate of the treatment difference and its precision based on the assumption of homogeneity across studies, i.e. the treatment effect is consistent across studies. However, if the treatment effect is not the same in different studies then the precision of the estimate of treatment effect will be too small since it does not include any between study component of variability. This heterogeneity of effect between studies can be allowed for (see, for example, [18]) and this will lead to wider confidence intervals for treatment contrasts compared to those under the assumption of homogeneity. The tolerance interval is a different concept which provides the likely range for the outcome of new studies. According to van Houwelingen [19], if this interval contains zero, the sign of the result of a future study is hard to predict, that is, it provides the distribution of individual study effects based on the between study variability not the precision of the estimate of overall treatment effect. In clinical research, it is unreasonable to expect the outcome of all future studies to be directionally the same and the conclusion of effect should not be based on this interval.

The Second Poster

The Second Poster was presented at the meeting of the American Thoracic Society in 2003 [13]. As with the first it was entitled ‘Inhaled sodium cromoglycate in children with asthma: systematic review.’ It had the same authors but in a different order and with one new name.

The selection criteria were not detailed and the primary outcome measure was now the proportion of symptom-free days. As with the paper in Thorax, 24 studies were included. However, seven studies that had been included in the review published in Thorax were not included and seven new studies that had not been included in either the First Poster or in the Thorax Paper were now included. All the new studies would have been available to the authors before the presentation of the First Poster in 1999. Only four studies contributed to the primary outcome measure. The conclusion was ‘There is insufficient evidence for a beneficial effect of DSCG compared to placebo.’

The poster appeared to be based on a Cochrane Review subsequently published in 2003 and discussed further below.

The Cochrane Collaboration Review

The Cochrane Collaboration is recognized internationally as a forum for reporting systematic reviews and provides both guidelines and tools for carrying out such reviews. The authors of the previously mentioned initial poster and paper followed up their work by producing a systematic review for the Cochrane Library [14] in 2003. This review used the same studies and had the same authors presented as for the Second Poster.

The review incorporated a more rigorous literature review than the original paper and also included a wide range of outcome variables, including the two symptoms of cough and wheeze previously reported. The inclusion criteria for studies appeared to have changed in that studies with co-interventions (other than rescue medications as needed), e.g. studies in which isoprenaline and/or corticosteroids (oral or inhaled) were being administered in fixed dosage to the SCG and placebo arms of the study, were excluded. As with the paper, a total of 24 studies were included. However, the change in inclusion criteria resulted

![Figure 2. Pre-school versus school children.](image-url)
The primary outcome variable was declared as ‘proportion of symptom-free days’ although it was not clear why or when it was determined that this should be the primary outcome compared to symptoms of cough and wheeze as previously reported. There were 16 secondary outcome variables. Although 24 studies were listed as being included, three are not used in any of the analyses (Collins 1971, Easton 1973, Tuchinda 1974). Collins 1971 and Tuchinda 1974 included children on regular oral steroids. In Collins 1971, in the group not on steroids, 5/9 outcome measures were significantly in favour of SCG including number of attacks, hours of wheezing, breathlessness, times awakened and cough. Tuchinda 1974 had one outcome measure out of four, medication use, significantly in favour of SCG. Easton 1973 did not record the age of children included, had only one outcome measure, change in blood eosinophils, significantly in favour of SCG.

The primary variable of symptom-free days was reported in only four of the 24 studies. For this variable there was no statistically significant difference between SCG and placebo, and the review stated that ‘Although limited by the small number of trials, there is no evidence to support the superiority of SCG over placebo in the proportion of symptom-free days, the main outcome of this review.’ The conclusion was generalized to ‘There is insufficient evidence for a beneficial effect of SCG compared to placebo.’ To determine the robustness of this conclusion, it is important to look in detail at both the primary outcome variable and also secondary outcome measures. It is clearly difficult to understand how the primary outcome variable which is based on only four studies can be considered representative of the 24 studies included. Even accepting this, three of these four studies were directionally in favour of SCG, one of which was statistically significant. The fourth study [20] was directionally in favour of placebo (after adjustment for baseline, but not without adjustment) and included 218/292 (75%) of the patients in the four trials and was itself at the time of publication and subsequently, challenged regarding the method of drug administration [21,22]. Thus, the conclusion of this systematic review appears to be based predominantly on the results of a single study in the younger age group (age range 1–4 years) with a questionable mode of drug delivery. Details of the studies included in the primary outcome measure are provided in Table I.

Do the secondary variables support the conclusion? The authors quote ‘Most secondary outcome measures, namely day cough, day wheeze, use of rescue oral steroids and hospital admission failed to reveal any significant group differences between SCG and placebo.’ Note, however, that day wheeze and use of rescue oral steroids were both

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Difference (%) (SCG-placebo)</th>
<th>95% CI</th>
<th>Length of each treatment period</th>
<th>Symptom-free days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SCG</td>
</tr>
<tr>
<td>Cogswell</td>
<td>24</td>
<td>11.1</td>
<td>0.5, 21.7</td>
<td>6 months</td>
<td>60.7%</td>
</tr>
<tr>
<td>Edmunds</td>
<td>30</td>
<td>15.0</td>
<td>-0.3, 30.3</td>
<td>4 weeks</td>
<td>47 ± 7%</td>
</tr>
<tr>
<td>Henry</td>
<td>20</td>
<td>8.0</td>
<td>-5.5, 21.5</td>
<td>2 months</td>
<td>25 days</td>
</tr>
<tr>
<td>Tasche</td>
<td>218</td>
<td>-1.6</td>
<td>-7.7, 4.6</td>
<td>5 months</td>
<td>Range 0–50</td>
</tr>
</tbody>
</table>

Unadjusted means quoted in paper are in favour of SCG; difference and CI are adjusted and in favour of placebo.
From Table II, it is immediately apparent that six outcome variables were represented in more studies than the primary outcome variable. Since detection of significant effects is related to the number of studies included, it is reasonable to assume that other outcome variables might have

**Table II. Summary of primary and secondary outcome variables.**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Number of studies</th>
<th>Mean difference(^t) (95% CI)</th>
<th>Statistically significant</th>
<th>Number of studies favouring SCG</th>
<th>Number of studies favouring placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall symptom severity</td>
<td>11</td>
<td>(-0.19) ((-0.32, -0.07))</td>
<td>Yes</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Day wheeze</td>
<td>10</td>
<td>(-0.11) ((-0.19, -0.03))</td>
<td>Yes</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Bronchoditator use</td>
<td>10</td>
<td>(-0.24) ((-0.42, -0.07))</td>
<td>Yes</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Day cough</td>
<td>9</td>
<td>(-0.18) ((-0.32, 0.04))</td>
<td>No</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Steroid use</td>
<td>7</td>
<td>(-0.19) ((-0.27, -0.12))</td>
<td>Yes</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Night cough</td>
<td>5</td>
<td>(-0.13) ((-0.19, -0.03))</td>
<td>Yes</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Day activity</td>
<td>4</td>
<td>3.57 (11.8, 8.32)</td>
<td>No</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Symptom-free days</td>
<td>4</td>
<td>(-0.02) (0.03, 0.08)</td>
<td>No</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Night wheeze</td>
<td>3</td>
<td>(-0.29) ((-0.48, -0.10))</td>
<td>Yes</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>3</td>
<td>0.72 (0.62, 0.82)</td>
<td>Yes</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>3</td>
<td>(-0.30) ((-0.71, 0.10))</td>
<td>No</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Proportion of patient preferences for SCG over placebo(^t)</td>
<td>2</td>
<td>0.81 (0.71, 0.90)</td>
<td>No</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Proportion of clinician preferences for SCG over placebo(^t)</td>
<td>2</td>
<td>(-0.26) ((-0.59, 0.06))</td>
<td>Yes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Day asthma</td>
<td>2</td>
<td>1.16 (0.60, 1.71)</td>
<td>No</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Night asthma</td>
<td>2</td>
<td>(-0.39) ((-0.81, 0.04))</td>
<td>No</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Success rate (odds ratio)</td>
<td>2</td>
<td>(-0.30) ((-0.71, 0.10))</td>
<td>No</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Auscultation</td>
<td>2</td>
<td>(-0.26) ((-0.59, 0.06))</td>
<td>Yes</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td></td>
<td></td>
<td>30</td>
<td>12</td>
</tr>
</tbody>
</table>

*All outcomes converted to 0–3 scale, except symptom-free days (percentage), hospital admissions, patient and clinician preferences (proportion) and success rate (odds ratio).

\(^t\)All estimates except sleep disturbance in favour of SCG.

\(^t\) Patient and clinician preferences from crossover trials.
greater power to detect effects than ‘symptom-free days.’

Out of the 16 secondary variables listed in Table II, eight are statistically significant in favour of SCG, none are statistically significant in favour of placebo. Indeed, out of the five secondary variables statistically analysed, and represented by more studies than the primary variable, four were statistically significant. Table II also gives for information the number of directional differences for the two treatments for each outcome variable and over all outcome variables. Thus, 69 contrasts favoured SCG (30 were statistically significant) and 12 contrasts favoured placebo (none were statistically significant). It should be noted that these contrasts are not completely independent but nevertheless the totality of information in Table II would indicate that far from ‘most secondary outcome variables failed to reveal any significant group differences’ there is very clear evidence that SCG provides additional benefit compared to placebo over a range of asthma symptoms and other outcome measures in childhood asthma.

Table III. Studies excluded from Cochrane Review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation of SCG</th>
<th>Reason for exclusion</th>
<th>Outcome of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (1968)</td>
<td>Dry powder</td>
<td>Isoprenaline control</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Sly (1970)</td>
<td>Dry powder</td>
<td>2/21 patients used steroids continuously</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Fox (1972)</td>
<td>Dry powder</td>
<td>Nine patients on regular steroids</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Silverman (1972)</td>
<td>Dry powder</td>
<td>Isoprenaline control</td>
<td>Significantly in favour of SCG for ‘failure’ at 12 months</td>
</tr>
<tr>
<td>Bernstein (1972)</td>
<td>Dry powder</td>
<td>Above age range and continuous steroids allowed</td>
<td>Patient preference reported for 151 children &lt;17 years – significantly in favour of SCG</td>
</tr>
<tr>
<td>Hyde (1973)</td>
<td>Dry powder</td>
<td>15/57 patients on daily steroids</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>McLean (1973)</td>
<td>Dry powder</td>
<td>Included children &gt;18 years</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Crisp (1974)</td>
<td>Dry powder</td>
<td>Steroid use allowed</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Lecks (1974)</td>
<td>Dry powder</td>
<td>Included children &gt;17 years, possibly &gt;18 years</td>
<td>96/105 patients &lt;17 years old – no outcome data available</td>
</tr>
<tr>
<td>Berman (1975)</td>
<td>Dry powder</td>
<td>Age range 0–18 years</td>
<td>14/276 patients over 17 years, none over 18 years – significantly in favour of SCG</td>
</tr>
<tr>
<td>Sellars (1975)</td>
<td>Dry powder</td>
<td>Included children &gt;17 years, possibly &gt;18 years</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Miraglia et al. (1982)</td>
<td>Nebulizer 1 mg MDI</td>
<td>10/31 patients used steroids continuously</td>
<td>Significantly in favour of SCG</td>
</tr>
<tr>
<td>Selcow (1989)</td>
<td></td>
<td>Age range 8–20 (mean c 13 years)</td>
<td>Significantly in favour of SCG</td>
</tr>
</tbody>
</table>

It should be emphasized that this interpretation and conclusion is based on the data as presented in the Cochrane Review. However, 13 studies were excluded since they did not satisfy the selection criteria for the review yet nevertheless provide additional information. Reasons for exclusion were primarily that the age range exceeded 18 years (five studies), patients were receiving regular steroid therapy (six studies) and finally the control group was isoprenaline (two studies). We question whether studies falling into the last two categories should have been excluded. Firstly, the amount of isoprenaline and the dose of oral steroids remained fixed throughout the study. Secondly, in many studies patients are not removed from their existing medications, rather patients have the test treatments added. The 13 studies excluded and their outcomes are detailed in Table III.

The studies enrolled a large number of patients, the majority of whom satisfied the criteria for inclusion in the review. As can be seen from Table III, 12 out of the 13 studies had outcome
variables which were statistically significantly in favour of SCG.

Further, the review fails to bring out strongly enough the confounding factors of age and mode of administration on outcome although they do acknowledge that ‘studies that included children below the age of 5 years showed less effect than studies that (also) included older children’ and ‘studies that applied nebulized SCG showed less effect than studies that showed other ways of administration.’

THE CONSEQUENCES

The consequences of these reviews have been substantial for the use of SCG in childhood asthma. Prior to this review, several guidelines for the management of childhood asthma had been published by international consensus groups recommending SCG as maintenance treatment for children with moderate asthma [23,24]. Additionally, in the Guidelines produced by the British Thoracic Society published in 1997, SCG and inhaled steroids were both recommended as first choice preventative treatment in young children [25]. All this changed when the poster presented at ATS was used to demonstrate that SCG had no role to play in the treatment of childhood asthma. The subsequent paper published in Thorax (2000) was the main factor leading to the statement in the British Guideline on the Management of Asthma [26] that ‘sodium cromoglicate is ineffective in children.’ Although no reference was given, we understand that a reference to the paper should have been cited. The Cochrane Review appeared to be the main basis on which SCG was removed from the WHO Model List of Essential Drugs [27].

DISCUSSION

In recent years there has been a plethora of meta-analyses or systematic reviews of interventions. These are invariably held up as ‘evidence-based’ examples of the effectiveness or otherwise of the intervention. There is no doubt that these analyses do have a role in modern-day decision making but there are many dangers inherent in these approaches. Here, we have an example of a systematic review being repeated on four occasions with varying studies included and varying endpoints to demonstrate that SCG should no longer be recommended for use in childhood asthma.

One important characteristic of all four presentations is that several large studies have been identified which could have contributed to the overall analysis but which have been omitted. Many of these studies were statistically significantly in favour of SCG compared to placebo and some were even considered to be the pivotal studies for regulatory submissions. A major assumption of systematic reviews is that the selection criteria should be appropriate and that all studies satisfying the selection criteria should be included to avoid or at least minimize the risk of bias, clearly in this case and despite the best endeavours of the authors of the reviews this has not been achieved.

A second important point related to meta-analyses is that both the methodology and the conclusions are appropriate to the data. Meta-analyses bring together data from many published sources and it is rarely possible for authors of such reviews to go back to the original individual subject data and they are therefore reliant on the information available in the relevant publications. These may not include all the information necessary for the meta-analysis and may indeed provide no quantitative information on some of the outcome variables. This provides a great challenge to the meta-analyst who wants to include as many studies as possible to avoid criticisms of bias and yet at the same time wishes to minimize the assumptions made in deriving the necessary estimates for inclusion of the study in the analysis. In the poster and paper versions of these reviews, wheeze and cough are presented as the outcome measures of interest. However, it is apparent from the paper that cough and wheeze were not separately reported in all studies, rather a composite symptom score was reported. For these studies, the same overall symptom score was used
for both cough and wheeze. It is therefore of little surprise that both outcome variables show a similar response, but more importantly it becomes much more difficult to describe these as effects on ‘cough’ and effects on ‘wheeze’ or to interpret the size of effect in clinical terms. For both outcome variables, the 95% confidence intervals for the differences between treatments, allowing for heterogeneity between studies, do not include zero which would in most cases lead to the conclusion of a demonstrated effect of the drug rather than the converse conclusion reached in the paper. The conclusion of the authors focused mainly on the tolerance interval which, assuming a normal distribution, predicts the range of effects that would be seen for the outcome of future studies. Quantitative interactions between treatment and study are a priori very plausible whereas qualitative interactions may be considered implausible [28,29]. In this respect, if the tolerance interval includes zero but the overall effect is significant, a transformation of the data may be appropriate to restore additivity [28]. Alternatively, if qualitative interactions are thought to exist, then these could be tested using formal methods such as Gail–Simon [29]. We feel that ‘tolerance interval’ is inappropriate for answering the simple question of whether one drug improves efficacy compared to another. Indeed it would appear illogical to conclude that a treatment is not efficacious just because in a minority of trials it would show no efficacy.

Heterogeneity of response was detected in several outcome measures and this should be no surprise for a number of reasons. Firstly, studies have included children from a wide age range (e.g. studies in the age range 0–1 year and also in the age range 7–17 years). Patients might be expected to have completely different aetiologies over such a wide range and even the confidence in the diagnosis of asthma would differ markedly. Secondly, the assessment tools themselves would be different (e.g. administered by parents for some children in the lower age ranges). Thirdly, the time frame considered coincided with a period over which new methods of administration of SCG were being developed, with the resulting likelihood that different effective doses were administered. The review did identify a reducing effect of SCG with time of publication – this was confounded with both method of administration and age of child. The earlier studies were carried out with the dry powder formulation and in older children, whereas the later studies tended to be nebulizer/aerosol formulations in younger children. Further investigation of these aspects would indicate an even stronger effect of SCG in older children. This was suggested in a letter to Thorax by Professor Silverman [30] following the publication of the Thorax review but refuted by the authors. The data they presented suggested otherwise as was shown in a subsequent letter from ourselves [31].

The final systematic review was carried out under the auspices of the Cochrane Collaboration, considered by many to be the ‘gold standard’ for evidence-based medicine. This provided one final twist. The review was more wide-ranging than that reported in the Thorax review paper in that many more outcome variables (17 in total) were reviewed. However, the primary variable was declared as ‘proportion of symptom free days’ and all other outcome variables (including cough and wheeze) were considered as secondary. The primary variable was available for only four studies, one of which contributed over 75% of the patients. The overall conclusion was based on this outcome variable, with little weight given to the fact that eight of the secondary variables were statistically significantly in favour of SCG. In summary, the conclusion drawn from the Cochrane Collaboration review was based primarily on the outcome of a single study.

Other factors which influenced the conclusions reached in the systematic reviews were the potential for bias due to the absence of small negative studies and the size of effect. The possibility of bias was examined via the use of funnel plots. These plots were by no means conclusive (see Figure 3) and did not overly support the concerns of the authors – indeed there was greater potential bias through the omission of 13 studies, mostly in the older age group and using the dry powder formulation, of which eight were significantly in favour of SCG. The size of effect is...
of course important and there is clearly a difference between statistical significance and clinical relevance. Systematic reviews through their more precise estimates of treatment effect have the potential of providing statistically significant results which have no clinical relevance. Studies in paediatrics are recognized as being difficult to conduct and in asthma most of the symptom assessments are subjective in nature. Childhood asthma is characterized by symptom-free days and consequently mean scores over a period of treatment are likely to be relatively low based on 0–3 symptom scales. This of course does speak for the use of symptom-free days as an outcome variable on which it is much easier to place a clinical interpretation, but in the case of the Cochrane Review only four studies contained this information. As the authors of the systematic reviews pointed out, mean symptom scores are generally low due to dilution by symptom-free days. This combined with the fact that clinical trials in the lower age group (up to 5 years old) were only conducted in children with relatively mild disease and less certain diagnoses does mean that the statistically significant effects shown in these analyses may well have clinical relevance and cannot be dismissed as small without further justification.

We and others in the respiratory field felt strongly that the conclusions drawn from each of these reviews were flawed and inappropriate. Our concerns were reflected in a number of letters and other communications [31–34]. We have achieved some minor changes to the BTS guidelines. The 2003 Guidelines stated 'sodium cromoglicate is ineffective in children.' This was changed in the 2004 update [35] to ‘The evidence of benefits of sodium cromoglicate in children is contentious. This is under active review’ and in the 2005 update [36] to ‘Sodium cromoglicate is of some benefit in adults and is effective in children aged 5–12. There is no clear benefit with SCG in children aged <5.’ However, this is virtually the only mention of SCG in the Guideline. There is no recommendation for its usage.

Additionally, there was a subtle change in the wording of the conclusions in the four publications:

Poster 1: ‘This review provides no evidence for a beneficial effect of sodium cromoglicate in children with asthma.’

Thorax Review Paper: ‘There is insufficient evidence that sodium cromoglicate has a beneficial effect as maintenance treatment in children with asthma.’

Poster 2: ‘There is insufficient evidence for a beneficial effect of SCG compared to placebo.’

Cochrane Review: ‘There is insufficient evidence to determine if sodium cromoglicate is more beneficial than placebo in the treatment of childhood asthma.’

However, the message is clear – once in print it is difficult to change perceptions. The consequence in this case is that there is the likelihood that SCG is removed as a treatment option for childhood asthma despite its regulatory approval, its use over many years and its undoubted and arguably unrivalled safety profile, and that children will be denied the potential benefits.

It would be nice to think that this is an isolated case of a potentially unreliable but influential systematic review. However, there are several examples in the public domain including a review of short course versus long course antibiotics in otitis media carried out by Kozyrskyj et al. [37] and a review of inhaled corticosteroids carried out by Rowe et al. [38]. Both of them counted data twice and are discussed by Senn [39,40]. A more recent example is the Cochrane Collaboration.
overview of antivirals published by Jefferson et al. [41]. Keene [42] pointed out that this review focused ‘on one subsidiary endpoint for the prophylaxis trials never previously considered particularly important and not generally included in trials even as a secondary endpoint’ and the ‘analyses they themselves present show antivirals are effective’ in treatment trials even though they conclude antivirals cannot treat influenza-like symptoms. In addition ‘several well-conducted phase II double-blind trials are discarded.’

There is a great onus on all those involved in the conduct and reporting of systematic reviews to ensure the appropriateness of the methodology used and conclusions drawn otherwise we will continue to deny the possibility of patients receiving safe and effective therapies.

Despite the different selection criteria used for the reviews and the omission of many useful positive studies, it is worthy of note that all overwhelmingly confirm that SCG does have an effect in childhood asthma, more so for older children using primarily the dry powder formulation. SCG has been wrongly labelled as ineffective in childhood asthma through the misuse and misinterpretation of the available data.

CONCLUSION

The review of the four publications discussed above has brought out three major criticisms:

1. No justification is given for the exclusion of a number of relatively large and positive placebo-controlled studies, nor for why trials have been removed.

2. The analyses presented provide a misleading picture of the use of SCG in children in that no allowance has been made for grouping together of widely different age groups or methods of administration of SCG.

3. The conclusions are not justified, nor supported, by the data and analyses provided. On the contrary, the evidence reviewed demonstrates that inhaled sodium cromoglicate is an effective therapy in childhood asthma.

All these reviews have been through a review process. The processes should be examined to ensure that reviews with wide-ranging prescribing implications are methodologically correct and draw the right conclusions.

CONFLICT OF INTEREST

M. T. Stevens and A. M. Edwards were employed by Fisons Pharmaceuticals until 1996; J. B. L. Howell was involved in the early clinical development of sodium cromoglicate.

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