

# The combination of nebulized sodium cromoglycate and salbutamol in the treatment of moderate-to-severe asthma in children

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The aim of this multi-centre prospective study was to evaluate the efficacy, tolerability, and safety of the combination of sodium cromoglycate (SCG) and salbutamol (administered as a nebulized solution), compared to SCG alone and salbutamol alone, in the management of severe, intractable asthma in childhood. The study was an open, randomized, cross-over trial of 12 weeks' duration in children with moderate-to-severe intractable asthma. All treatments were administered twice daily by powered nebulizer. The primary outcome measure was the change in asthma severity, as measured by the mean asthma score during the last 2 weeks of a baseline period and the last 2 weeks of each treatment. Secondary outcome measure was the patient's opinion of the effectiveness of treatment. The change in asthma scores from baseline values were significantly greater with the combination treatment compared to each component administered separately. The mean difference in asthma score between the combination and salbutamol was:  $-7.5$ ; 95% CI,  $-11.70$  to  $-3.29$  ( $p < 0.0001$ ). The mean difference between the combination and SCG was:  $-8.53$ ; 95% CI,  $-14.03$  to  $-3.25$  ( $p < 0.0001$ ). Patients were also significantly in favor of combination treatment ( $p < 0.001$  vs. salbutamol;  $p < 0.01$  vs. SCG). Two patients reported adverse effects. We concluded that regular twice-daily inhalation of a combination of SCG and salbutamol gave better control of symptoms than previous treatments in patients with severe, intractable asthma. Few adverse effects with this therapy suggest that it is extremely useful, safe, and effective.

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Despite the availability of new potent bronchodilators, inhaled corticosteroids, and anti-allergy drugs, there are still children with moderate and severe asthma who are difficult to treat. Many of these children require combinations of drugs and frequent hospital admissions. The Japanese guidelines on the preventative drug therapy of childhood asthma (1) recommend the combination of a  $\beta_2$ -agonist and sodium cromoglycate (SCG) to be inhaled twice daily as a nebulized solution in the treatment of moderate symptoms. This treatment is also recommended as the first step for treatment of severe symptoms and is increased to four times daily in the second step of severe symptoms and for intractable cases. Nishikawa et al. first

reported excellent results with the use of this combination (2). Following this report, the Severe Asthma Inhalation Research Committee of Japan organized a multi-centre clinical trial to investigate the safety, efficacy, and tolerability of this treatment. The results are presented in this article.

## Materials and methods

### Study design

The trial was a randomized, open, cross-over design in which the combination of SCG plus salbutamol was compared with either salbutamol alone or with SCG alone (Fig. 1).

## Methods

After a 4-week baseline period, during which existing treatment was continued, patients were randomized to receive either the combination as first treatment, with the single-drug comparator as second treatment (Groups A2 and B1), or the combination as second treatment and the comparator treatment first (Groups A1 and B2). Each treatment period was for 4 weeks and the total trial period for each patient was 12 weeks. The randomization of treatment allocation was managed by an independent central controller who did not have contact with any of the subjects entered. He supplied each center with numbered envelopes for allocation of patients to treatment groups A1, A2, B1, or B2. Treatment allocations were randomized in blocks of eight and each hospital center received instructions for eight subjects, with two subjects allocated to each treatment order group. At each center, the envelopes were opened from the lowest number, as patients were admitted into the trial, and were treated in accordance with the directions therein. Patients at any one center could be allocated to any of the four treatment groups.

## Subjects

The subjects were patients with moderate and severe asthma, of either gender and <20 years of age, whose asthma had proved difficult to control and in whom inhalation therapy using a powered nebulizer was possible. The definitions of moderate and severe asthma were those used by the Japanese Society of Pediatric Allergy and Clinical Immunology, as follows. Moderate asthma is defined as the subject having had either mild attacks of asthma two or three times in a month, moderate attacks two or three times in 6 months, or severe attacks two or three times in a year. Severe asthma is defined as the subject having had moderate or severe attacks two or three times in a month or severe attacks two or three times in 6 months. A severe asthma attack is one in which wheezing, dyspnoea, and cyanosis are present and activities such as play, sleep, speech, and eating are difficult or impossible. A moderate attack is one in which there is wheezing and dyspnoea and activities are slightly difficult. A mild attack is one in which there is slight wheezing and activities are normal.

For inclusion in the study, patients had to have allergic or non-allergic perennial asthma. Patients were excluded if they were being treated with regular inhalations of solutions of SCG or salbutamol or with long-acting injected corticosteroids. Patients or their parents had to keep

asthma diary cards throughout the 12 weeks of the trial.

## Test treatments

Test treatments were given in addition to existing treatment. Each test treatment consisted of 2–2.2 ml of nebulizer solution delivered over 5–10 min using a powered jet nebulizer supplied by Nippon Shoji (Aswell Inc., Chuo-ku, Osaka, Japan). Treatments were administered twice daily by inhalation. The treatments compared in Groups A1 and A2 were: 2 ml of physiological saline to which was added either 0.1 ml of a 5-mg/ml aqueous solution of salbutamol (for children <6 years of age) or 0.2 ml of salbutamol solution (for children ≥ 6 years of age); or 2 ml of a 1% aqueous solution of SCG with 0.1 or 0.2 ml of salbutamol solution added in the same manner as for the saline. For Groups B1 and B2 the treatments compared were: 2 ml of a 1% aqueous solution of SCG; or 2 ml of a 1% aqueous solution of SCG to which was added either 0.1 ml of a 5-mg/ml aqueous solution of salbutamol (for children <6 years of age) or 0.2 ml of salbutamol solution (for children ≥ 6 years of age). In most cases the nebulized cloud was inhaled through a mouthpiece, except in the case of young children, who used a facemask.

## Concomitant treatments

Drugs used during the baseline period were continued throughout both test periods. The dose of these drugs could be varied at the discretion of the investigator. The names, doses, and number of doses of all concomitant drugs were recorded on the daily diary card.

## Measurements

The primary outcome measure was the daily asthma score. The asthma score is the sum of the attack score and the treatment score. The attack score was based on the information from the daily diary cards completed by the parent, guardian or patient. They recorded the severity of asthma symptoms experienced during three time-periods of each day (morning, afternoon, and evening) using the following scale: 0, no attack; 1, mild attack; 2, moderate attack; and 3, severe attack. They also recorded the treatment(s) used each day, including any additional treatments needed to deal with acute symptoms. From these records the physician dealing with the patient calculated the daily attack score, scoring mild attacks as 1, moderate attacks as 2, and severe attacks as 3. The treatment score was

|          | Baseline period       | Treatment<br>Period 1  | Crossover | Treatment<br>Period 2  |
|----------|-----------------------|------------------------|-----------|------------------------|
|          | 4 weeks               | 4 weeks                |           | 4 weeks                |
| Group A1 | Existing<br>treatment | Salbutamol +<br>saline | ✕         | SCG +<br>salbutamol    |
| Group A2 | Existing<br>treatment | SCG +<br>salbutamol    | ✕         | Salbutamol +<br>saline |
| Group B1 | Existing<br>treatment | SCG +<br>salbutamol    | ✕         | SCG                    |
| Group B2 | Existing<br>treatment | SCG                    | ✕         | SCG +<br>salbutamol    |

Fig. 1. Trial design showing the treatment given during each 4-week period of the 12-week trial in each of the four treatment groups. SCG, sodium cromoglycate.

calculated by adding the scores for each treatment given each day using a scoring system in which unit doses of drugs are given a score (e.g. inhaled Salbutamol 100 µg-l: oral prednisolone 5 mg-5). Both the system for arriving at the attack score and the treatment score have been standardized and developed by the Committee for the Evaluation of Asthma Severity appointed by the Japanese Society of Allergology.

#### Global assessment

At the end of each treatment period the patient/parent evaluated the effect of the treatment (regarding the severity of asthma) received for that period, compared to the baseline period, using the following scale:

- 1 = much better;
- 2 = better;
- 3 = slightly better;
- 4 = no change;
- 5 = worse; or
- 0 = don't know.

#### Side-effects

The type, degree, time of onset, duration, and treatment of any side-effect, together with recovery and possible causal relationship to treatment, were recorded by the investigator at the end of each treatment period.

#### Withdrawals

Patients could be withdrawn from the trial by the investigator if continuance was considered to be inappropriate. The time and reason for withdrawal were recorded. As far as possible patients were included in analyses up to the time of withdrawal.

#### Statistical analysis

The primary outcome measure was the severity of asthma as determined by the Asthma Score. This is the sum of the Daily Attack Score and the Daily Treatment Score and was calculated each week by the investigator from the daily diary cards kept by the patient or parent. The mean Asthma Score was then calculated for each patient for each 2-week period of the trial. Determining the change in mean Asthma Score for the last 2 weeks of the baseline to that for the last 2 weeks of each treatment period allowed a comparison to be made of the efficacy of test treatments. As each patient used both treatments, paired data were analysed using Wilcoxon Signed Rank Sum tests. As the order in which test treatments were administered were randomized, baseline values for each treatment order group were compared using the Mann-Whitney *U*-test. The other outcome measure was the opinion of the efficacy of each treatment provided at the end of the treatment period by the patient or parent. The numbers of patients falling into each of five categories were compared using the chi-square test. All tests were two-tailed and a *p*-value of less than 0.05 was regarded as significant. Data were analyzed using GraphPad™ Instat, Version 3.0, GraphPad Software Inc., San Diego, CA, USA).

#### Ethical approval

All patients or parents gave informed consent, and local ethical review committees gave approval for the trial.

#### Results

Two hundred and fifty-seven patients were entered into the study from 40 hospital centres, of whom 232 completed the trial and were included in the analysis. Details are given in Table 1. The mean age of the patients was 8.7 ( $\pm 3.5$ ) years. There were 150 males and 82 females. One hundred and forty-nine patients were classified as having severe asthma, and 81 patients had asthma that was moderately severe. Fifty-six subjects were in-patients throughout the trial, 157 were out-patients, and 17 were in-patients for part of the trial and out-patients for the remainder. The treatments used before the trial were: oral theophyllines (216 patients); oral  $\beta_2$ -agonists (152 patients); inhaled  $\beta_2$ -agonists (83 patients); inhaled corticosteroids (40 patients); oral corticosteroids (40 patients); and injected corticosteroids (20 patients). Mean ( $\pm$ SD) asthma scores for the last 2 weeks of the baseline period were: Group A1, 102.30 ( $\pm 66.27$ ); Group

Table 1. Characteristics of the patients

|                    | Group A1 (n=58) | Group A2 (n=59) | Group B1 (n=55) | Group B2 (n=60) | All patients (n=232) |
|--------------------|-----------------|-----------------|-----------------|-----------------|----------------------|
| Age: years*        | 8.4±3.7         | 8.8±3.7         | 9.0±3.4         | 8.7±3.4         | 8.7±3.5              |
| Gender             |                 |                 |                 |                 |                      |
| Male               | 40              | 40              | 33              | 37              | 150                  |
| Female             | 18              | 19              | 22              | 23              | 82                   |
| Height: cm*        | 127.5±22.3      | 129.1±18.7      | 130.9±19.4      | 131.4±20.0      | 129.7±20.0           |
| Weight: kg*        | 28.1±13.0       | 29.2±11.4       | 28.6±10.2       | 29.4±12.1       | 28.8±11.7            |
| Severity of asthma |                 |                 |                 |                 |                      |
| Severe             | 32              | 38              | 38              | 41              | 149                  |
| Moderate           | 26              | 20              | 16              | 19              | 81                   |
| Not recorded       | —               | 1               | 1               | —               | 2                    |
| Serum IgE†         | 834 (10–5,940)  | 693 (24–37,000) | 830 (20–5,000)  | 835 (7–4,830)   | 820 (7–37,000)       |
| Present treatment  |                 |                 |                 |                 |                      |
| Corticosteroids    | 10              | 10              | 11              | 17              | 48                   |
| Theophyllines      | 54              | 56              | 50              | 56              | 216                  |
| Beta-2 stimulants  | 58              | 59              | 55              | 60              | 232                  |

\*Data expressed as mean±SD.

†Data expressed as median (range).

A2, 122.79 ( $\pm 85.65$ ) (Mann–Whitney  $U$ -statistic 1458.0,  $p=0.279$ ). The baseline mean was as follows: Group B1, 127.28 ( $\pm 81.35$ ); Group B2, 109.01 ( $\pm 61.38$ ) (Mann–Whitney  $U$ -statistic 1398.5,  $p=0.2603$ ). Twenty-five patients were excluded from the analysis: nine did not complete either the baseline or the treatment periods; eight had inadequate records; three each had missing data or did not comply; and two dropped out for unspecified reasons.

The primary variable of treatment efficacy was the change in asthma scores from the values recorded during the last 2 weeks of the baseline to the values recorded during the last 2 weeks of each treatment period. Table 2 shows the change in the asthma score from the last 2 weeks of the baseline period to the last 2 weeks of the treatment period, the difference between the two treatment scores, and the  $p$ -value of the analysis of the difference (determined using the Wilcoxon Signed Ranks test). For this analysis the data from the subgroups in the two treatment order groups are combined. In Groups A1 and A2 the reduction in the mean ( $\pm$ SD) asthma score was 43.90 ( $\pm 39.9$ ) for the combination treatment and 36.77 ( $\pm 43.01$ ) for salbutamol alone. In Groups B1 and B2 the reduction was 45.38 ( $\pm 47.20$ ) for the combination and 36.75 (45.62), for SCG alone. In both cases the mean difference in the reduction in asthma scores was significantly greater for the combination than for the single treatments; between the combination and salbutamol the mean ( $\pm$ SD) difference was 7.5 ( $\pm 22.6$ ) ( $p < 0.001$ ) and between the combination and SCG 8.5 ( $\pm 28.5$ ) ( $p < 0.001$ ). The mean asthma scores for each 2-week period of the study are shown in Fig. 2.

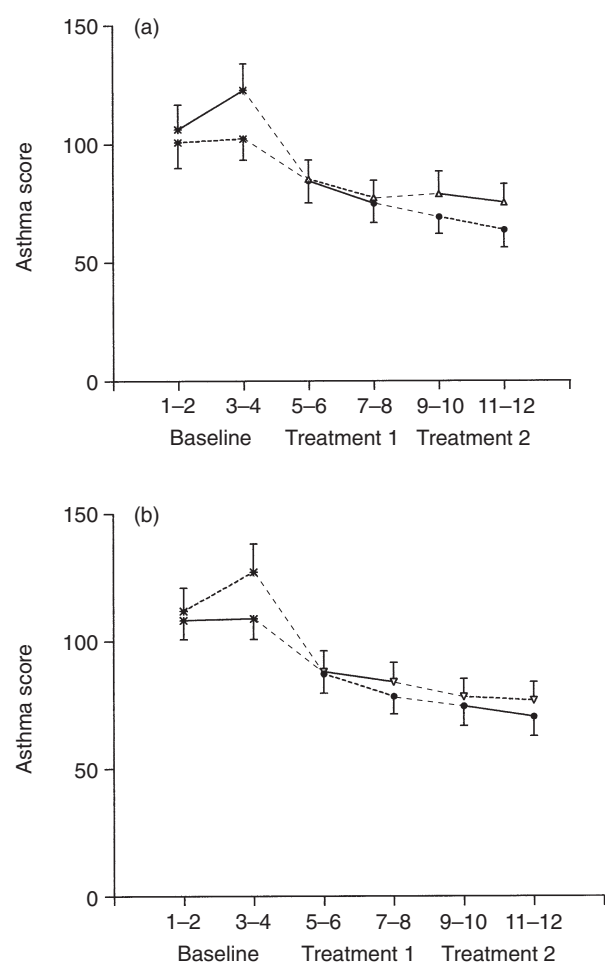


Fig. 2. Mean asthma scores for each 2-week period of the study. (a) Groups A1 and A2. (b) Groups B1 and B2. (a) \*—\*, baseline A1; \*—\*, baseline A2.  $\Delta$ — $\Delta$ , A1 treatment salbutamol.  $\bullet$ — $\bullet$ , A1 treatment 2 SCG/salbutamol.  $\bullet$ — $\bullet$ , A2 treatment 1 SCG/salbutamol.  $\Delta$ — $\Delta$ , A2 treatment 2 salbutamol. (b) \*—\*, baseline B1; \*—\*, baseline B2.  $\bullet$ — $\bullet$ , B1 treatment 1 SCG/salbutamol.  $\nabla$ — $\nabla$ , B1 treatment 2 SCG.  $\nabla$ — $\nabla$ , B2 treatment 1 SCG.  $\bullet$ — $\bullet$ , B2 treatment 2 SCG/salbutamol.

Table 2 Asthma scores: Groups A1/A2 and B1/B2

| Treatment group | Baseline: mean (SD)  | Final 2 weeks Mean (SD) |                | Final 2 weeks Mean (SD) |                | Change from baseline Mean (SD) |                | Difference (95% CI)                                | Wilcoxon p-value   |
|-----------------|----------------------|-------------------------|----------------|-------------------------|----------------|--------------------------------|----------------|----------------------------------------------------|--------------------|
|                 |                      | Salbutamol              | SCG/Salbutamol | SCG                     | SCG/Salbutamol | SCG/Salbutamol                 | Salbutamol     |                                                    |                    |
| Group A1/A2     | 112.81 (77.18) n=115 | 76.36 (57.62)           | 69.51 (59.08)  | 80.62 (55.93)           | 74.47 (53.67)  | -43.9 (39.87)<br>-45.38 (7.20) | -36.77 (43.01) | -7.50 (-3.29 to -11.70)<br>-8.53 (-3.25 to -14.03) | <0.0001<br><0.0001 |
| Group B1/B2     | 117.90 (72.05) n=113 |                         |                |                         |                |                                |                |                                                    |                    |

SCG, sodium cromoglycate.

Table 3. Asthma scores: Change in asthma scores in Groups A1 and A2

| Treatment group | Baseline: mean (SD) | First treatment Mean (SD) |                | Second treatment Mean (SD) |                | Change from baseline Mean (SD) |                | Difference (95% CI)      | Wilcoxon p-value |
|-----------------|---------------------|---------------------------|----------------|----------------------------|----------------|--------------------------------|----------------|--------------------------|------------------|
|                 |                     | Salbutamol                | SCG/Salbutamol | Salbutamol                 | SCG/Salbutamol | Salbutamol                     | SCG/Salbutamol |                          |                  |
| Group A1        | 102.30 (66.27) n=56 | 77.45 (56.14)             |                |                            | 63.71 (55.05)  | -25.30 (30.94)                 | -39.72 (31.52) | -14.87 (-8.80 to -20.95) | <0.0001          |
| Group A2        | 122.79 (85.65) n=59 |                           | 74.92 (62.58)  | 75.33 (60.34)              |                | -47.46 (49.72)                 | -47.87 (46.36) | -0.41 (4.86 to -5.68)    | 0.5379           |

SCG = sodium cromoglycate

Table 4. Asthma scores: Change in asthma scores in Groups B1 and B2

| Treatment group | Baseline: mean (SD) | First treatment Mean (SD) |                | Second treatment Mean (SD) |                | Change from baseline Mean (SD) |                | Difference (95% CI)      | Wilcoxon p-value |
|-----------------|---------------------|---------------------------|----------------|----------------------------|----------------|--------------------------------|----------------|--------------------------|------------------|
|                 |                     | Salbutamol                | SCG/Salbutamol | Salbutamol                 | SCG/Salbutamol | Salbutamol                     | SCG/Salbutamol |                          |                  |
| Group B1        | 127.28 (81.35) n=55 |                           | 78.50 (51.50)  | 76.89 (52.95)              | 70.49 (56.02)  | -49.45 (54.01)                 | -48.78 (55.46) | 0.82 (5.50 to -3.85)     | 0.8886           |
| Group B2        | 109.01 (61.38) n=58 | 84.09 (58.81)             |                |                            |                | -24.92 (32.31)                 | -42.17 (37.96) | -17.25 (-8.32 to -26.12) | <0.0001          |

SCG, sodium cromoglycate.

Table 5. Final opinion of patients of the effects of each treatment

|                 | SCG + salbutamol vs. salbutamol alone |            | SCG + salbutamol vs. SCG alone |        |
|-----------------|---------------------------------------|------------|--------------------------------|--------|
|                 | SCG + salbutamol                      | Salbutamol | SCG + salbutamol               | SCG    |
| Much better     | 57                                    | 29         | 56                             | 35     |
| Better          | 40                                    | 43         | 34                             | 39     |
| Slightly better | 11                                    | 21         | 16                             | 21     |
| No different    | 6                                     | 17         | 3                              | 14     |
| Worse           | 1                                     | 5          | 2                              | 4      |
| Chi-square      |                                       | 20.277     |                                | 13.632 |
| p-value         |                                       | <0.001     |                                | <0.01  |

Data are expressed as the number of patients in each category.  
SCG = sodium cromoglycate.

When the treatments were compared in the sub-groups according to treatment order, a carry-over effect was seen when the combination was the first treatment but not when it was the second. The results of this analysis are shown in Tables 3 and 4.

The patient's opinion of each treatment is shown in Table 5. Results are shown as number of patients for each category. The percentage of patients in Groups A1 and A2 who reported that they were better or much better was 84% for the combination and 63% for salbutamol ( $p < 0.001$ ): in Groups B1 and B2 it was 81% for the combination and 65% for SCG ( $p < 0.01$ ).

Adverse events were reported by two patients. One developed sneezing and nasal irritation with the combination treatment. This was of mild severity and treatment was not stopped. The second developed nausea when switched to the combination. This was severe and treatment was stopped. When procaterol was substituted for salbutamol the problem did not recur.

## Discussion

In this study the efficacy and safety of a combination of a solution of SCG and salbutamol inhaled twice daily using a powered nebulizer was compared to either salbutamol solution alone or SCG solution alone, in children with moderate and severe asthma.

The trial design can be criticized, as it was neither placebo controlled, nor double blind and did not include a washout period between treatments. We did not consider that a placebo treatment or a washout period was justified in this difficult-to-treat group of patients who were liable to unpredictable, severe attacks of asthma. Blinding was not possible as it was considered necessary to constitute the treatments fresh before each administration and the dose of added salbutamol varied according to age. To reduce the effects of these potential deficiencies in

the study, we used a strict randomization procedure managed by an independent central controller. The trial was conducted at 40 separate hospital centres. As the analysis of the characteristics of the four treatment groups shows that the randomization was satisfactory and the groups were comparable, we do not believe that the lack of a placebo and blinding compromised the results.

There have been few recent trials of a combination of SCG and a bronchodilator. The first SCG product, introduced into the UK in 1968, was a dry powder combination of SCG and the non-specific  $\beta$ -agonist, isoprenaline, and shown to give excellent results in both adults and children with moderate-to-severe asthma (3,4). The study by Silverman et al. (4), which compared SCG + isoprenaline with isoprenaline alone in children with severe perennial asthma, found that 71% of the combination-treated group were still well controlled after 1 year compared to 24% in the isoprenaline group. Shapiro et al. (5) compared nebulized SCG, terbutaline, and the combination of the two, in a double-blind cross-over study in 27 children with mild-to-moderate asthma. Significant differences between treatments were found in three out of 12 variables. Two of these were in favor of the combination and one in favor of SCG alone. The patients in this trial had relatively mild asthma and this, together with the fewer patient numbers, would make it difficult to demonstrate differences between active treatments.

We observed a carry-over effect when the combination was given as the first treatment, but not when it was the second treatment. This suggests that the beneficial effects of this treatment are prolonged after it is stopped, even when treatment that is shown to be significantly less beneficial is substituted. A similar carry-over effect was seen in an early trial by Kennedy (6) in adult asthmatic patients, comparing SCG + isoprenaline with isoprenaline alone, when the

combination was the first treatment. In two large multi-centre studies carried out in the USA comparing SCG with placebo, a carry-over effect was seen when SCG was the first treatment if no washout period was included (7) but not if a washout period was included (8).

We need to consider why this combined treatment is more effective as compared to the components administered alone. In addition to its anti-inflammatory effects, SCG has been reported to potentiate and sustain the smooth muscle relaxing properties of isoproterenol, epinephrine, and salbutamol (9). The two components of this combination may therefore have a true synergistic effect on the symptoms of asthma.

It has recently been shown that the protective effect of SCG against bronchial allergen challenge is dependent upon the dose delivered to the lung and the distribution of the drug within the lung (10). It is possible that administration using a nebulizer will give better distribution than a single dose administered from a dry powder or a metered dose aerosol and that the concomitant administration of a bronchodilating agent such as salbutamol will open the airways and allow better peripheral distribution. Iwasaki et al. (11) measured the amount of drug excreted in the urine for 4 h after administration of a 20-mg nebulized dose to children aged 0–16 years. As the amount appearing in the urine represents  $\approx 40\%$  of the dose deposited in the lung, it is possible to estimate the actual lung dose. They showed that it ranges from 0.5% (0.1 mg) of the delivered dose in infants 0–1 year of age and increases, according to age, to 2.4% (0.5 mg) in children aged 10–16 years. Hirota (12) has shown in 16 asthmatic children, 6–14 years of age, that when salbutamol is added to SCG solution, the mean 24-h urinary excretion is 1.53 times higher than with SCG alone. The mean excretion from SCG alone was 1.04% in his group of patients. These figures suggest that the addition of salbutamol increases the mean dose of SCG entering the lungs from 0.5 to 0.8 mg. This may be very important in terms of efficacy. It is normally recommended that SCG products should be administered four times a day. The dosing schedule in this trial was twice daily and the results show that this is adequate. Whether improved efficacy could be achieved by increasing the dose frequency is uncertain, but the potential for reduced compliance because of the inconvenience of a four-times-a-day schedule has to be taken into consideration. We believe that the efficacy demonstrated by the combination treatment is sufficient to recommend a twice-daily dosing. Current international guidelines (13)

recommend SCG alone only in mild persistent asthma in children above and below 5 years of age. There are no recommendations for its use in more severe asthma, and no consideration of its use in combination with other drugs, apart from in Japan. We suggest that the results of this trial justify considering its use in other countries in this group of difficult-to-treat patients.

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Competing Interests. Dr Alan Edwards was an employee of Fisons Pharmaceuticals Ltd. and is a consultant to Fujisawa Co. Ltd.

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