

Comparison between sodium cromoglycate (MDI: metered-dose inhaler) and beclomethasone dipropionate (MDI) in treatment of adult patients with mild to moderate bronchial asthma

A double-blind, double-dummy randomized, parallel-group study

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This study compared the efficacy and tolerability of sodium cromoglycate (SC) and beclomethasone dipropionate (BDP) in adult patients with bronchial asthma inadequately treated with bronchodilators alone. The study was a double-blind, randomized, double-dummy, parallel-group study. Patients with mild to moderate symptomatic asthma, inadequately treated with bronchodilators only, were, after a 2-week run-in (base-line) period, randomized to 8 weeks of treatment with either SC 10 mg four times daily or BDP 100 µg four times daily. Salbutamol metered-dose inhaler was given as relief medication. A total of 37 patients were randomized for treatment, 19 patients in the SC group and 18 patients in the BD group. Efficacy and safety were determined by daily record card data: morning and evening peak-expiratory-flow rates (PEFR), daytime and nighttime asthma symptom scores, and rescue salbutamol use. At clinic visits, FEV₁ and FVC were measured, as were the physician's and the patient's assessment of the medication at the end of the study. The safety and tolerability of the trial medication were assessed by monitoring adverse events throughout the study. A clinically and statistically significant improvement of the asthma in FEV₁, symptom scores, rescue medication, and global opinion of efficacy was observed, and both groups provided equivalent efficacy. The morning PEFR as well as the evening PEFR for both groups improved, but was statistically significant only for the BDP group (M-PEFR). Both drugs were well tolerated with only a few minor adverse events. This trial shows that SC and BDP are equally effective anti-inflammatory treatments for mild to moderate bronchial asthma in adults.

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The recognition that asthma is an inflammatory condition has led to the conclusion that most asthmatic patients need anti-inflammatory treatment in addition to bronchodilator therapy or a regular long-acting β_2 -agonist (2, 8, 16). The available anti-inflammatory drugs are inhaled corticosteroids, inhaled sodium cromoglycate (SC), and inhaled nedocromil sodium. SC – a nonsteroidal drug – is available as an aerosol delivering 5 mg (Lomuforte®)

per actuation, and initial studies have indicated that this formulation, at two puffs four times daily, offers a clinical advantage over the established formulation of 1 mg per actuation (4, 17).

No direct comparisons between inhaled SC (5 mg/dose) and inhaled beclomethasone dipropionate (BDP) in adults with mild to moderate asthma have been done. The purpose of this study was to compare the efficacy and tolerability of SC (10 mg four

times daily) and BDP (100 µg four times daily) in adult asthmatic patients with mild to moderate bronchial asthma whose symptoms were inadequately controlled by β_2 -agonists alone.

Material and methods

This study was a double-blind, randomized, double-dummy, parallel-group study. Patients with mild to moderate symptomatic asthma, inadequately treated with bronchodilators only, were, after a 2-week run-in (base-line) period, randomized to 8 weeks of treatment with *either* SC 5 mg/puff: 10 mg (2 puffs) four times daily and BDP placebo (2 puffs) four times daily, *or* BDP 50 µg/puff: 100 µg (2 puffs) four times daily and SC placebo (2 puffs) four times daily.

Salbutamol metered-dose inhaler (MDI) was given as relief medication. Efficacy and safety were determined by daily record card data: morning and evening peak-expiratory-flow rates (PEFR). Two symptom scores were recorded in the morning – asthma symptoms and tightness during the night – and two in the evening – asthma symptoms and cough during the day and rescue salbutamol use. Nighttime asthma symptoms were rated each morning according to the following five-point scale: 0 = none; 1 = awoke once because of asthma, cough, or both; did not use bronchodilator aerosol to get back to sleep; 2 = awoke once because of asthma, cough, or both; needed to use bronchodilator to get back to sleep; 3 = awoke once for longer than 1 h or awoke more than once because of asthma, cough, or both; 4 = awake most of the night because of asthma, cough, or both.

Each evening, the patients made a global rating of daytime asthma symptoms according to a five-point scale: 0 = none; 1 = occasional wheeze or breathlessness quickly relieved by bronchodilator aerosol; 2 = wheezing or short of breath most of the day which did not interfere with usual activities; 3 = wheezing or short of breath most of the day; some interference with usual activities; 4 = asthma very bad; could not go to work/school or do usual activities. At clinic visits, FEV₁ and FVC were measured, and the physician's and the patient's assessment of the medication were noted at the end of the study.

The safety and tolerability of the trial medication were assessed by monitoring adverse events throughout the study.

Patient characteristics (Table 1)

A total of 37 patients, 13 men and 24 women, were randomized for treatment. Their overall age was 43.95 years (mean), with a duration of asthma of 4.5 years (mean).

Table 1. Patient characteristics

Variable	SC	BDP	Total
No. randomized for trial	19	18	37
No. of men	9	4	13
No. of women	10	14	24
Age in yr (mean)	42.47	45.50	43.95
	SD = 13.50	SD = 10.45	SD = 12.05
	95% CI	95% CI	95% CI
	35.96, 48.98	40.30, 50.70	39.93, 47.96
Height cm (mean)	172.05	171.06	171.57
	SD = 11.14	SD = 6.82	SD = 9.18
	95% CI	95% CI	95% CI
	166.68, 177.42	167.66, 174.45	168.51, 174.63
Weight kg (mean)	72.79	68.78	70.84
	SD = 11.86	SD = 11.11	SD = 11.52
	95% CI	95% CI	95% CI
	67.07, 78.51	63.25, 74.31	67.00, 74.68
No. of atopics	13	9	22
No. of nonatopics	6	9	15
Duration of asthma (yr mean)	4.1	4.8	4.5
Relative FEV ₁ (%) at end of run-in	86.33	80.24	83.37
	SD = 14.42	SD = 19.50	SD = 17.12
	95% CI	95% CI	95% CI
	79.38, 93.28	70.42, 89.93	77.60, 89.07

SD = standard deviation; CI = confidence interval.

The overall relative FEV₁ was 83.37% (mean), and the reversibility in FEV₁, defined as percent increase of FEV₁ in 15 min after inhalation of 200 µg salbutamol, was 23% (mean).

Twenty-two (59%) patients were atopic, and 15 (41%) patients were nonatopic, as determined by skin prick test with 10 standard allergens (Table 1). This distribution of atopic and nonatopic patients between the SC and the BDP groups was not statistically significantly different (chi-square test with Yates correction: $P = 0.42$).

Four patients were excluded during the study. In the SC group, one patient was excluded for noncooperation, and one because of sudden worsening of the asthma. In the BDP group, one was excluded for noncooperation, and one because of a suspected adverse event (oral candidiasis).

Sixty-three percent of the patients in the SC group and 66% of the patients in the BDP group had nocturnal asthma, with a symptom score of at least 1, during the run-in period.

Inclusion criteria

Patients had to be between 18 and 65 years old inclusive, with a history of bronchial asthma for not less than 6 months, and to be symptomatic despite treatment with inhaled bronchodilators only. The asthma diary card score had to be a total of 10 or more for at least 7 days during the 14-day base-line

period. On entry to the trial, patients had to show reversibility of airways obstruction of at least 15% measured by FEV_1 in response to the inhalation of 200 µg salbutamol MDI, bronchodilators having been withheld during the 4 h before the test. Alternatively, patients who had shown greater than 20% variability in PEFR (either diurnal or day-to-day) over 1 week could be entered.

Concomitant therapy

Inhaled β_2 -agonist by MDI inhaler or dry powder taken when necessary was allowed as rescue medication, but not on a regular basis.

Statistics

For analysis of patient diary cards, the procedure described by O'Brien (Biometrics 1984: 40: 1079) was utilized. Other variables were analyzed by appropriate parametric methods (mainly *t*-test). The preselected significance level was 5% (two-sided). For the population mean, 95% confidence intervals (CI) were indicated. Patients' and clinicians' opinions of effectiveness were calculated by the Mann-Whitney U-test. The variables were all normally distributed (PDF test). For calculation of the variation of the PEFR and the FEV_1 , the relative values ((absolute value/predicted value) $\times$ 100)) were preferred to reduce the influence of the heterogeneity of age, height, and sex.

Results

Daily record card

PEFR. An improvement was observed in both the morning PEFR and the evening PEFR for both groups. In the SC group, the morning PEFR increased, not statistically significantly, with a mean of 2.5 l or 0.7% (relative) (base line to week 8) $P = 0.61$ (95% CI = -3.53, 2.13), and in the BDP group with a statistically significant mean of 39.8 l or 9.1% (relative) ((base line to week 8) $P = 0.001$ (95% CI = -14.08, -4.11)) throughout the study period. The difference between the two groups in morning PEFR values at the run-in period and at the 8-week period was not statistically significant (($P = 0.28$ (95% CI = -35.7, 114.2) and $P = 0.93$ (95% CI = -71.7, 78.1)). The difference between the two groups in the evening PEFR values at the run-in period and at the 8-week period was not statistically significant (($P = 0.90$ (95% CI = -12.26, 13.78) and $P = 0.42$ (95% CI = -18.88, 8.31)). The variation between the evening and morning PEFR did not change statistically significantly either for any of the groups (Fig. 1).

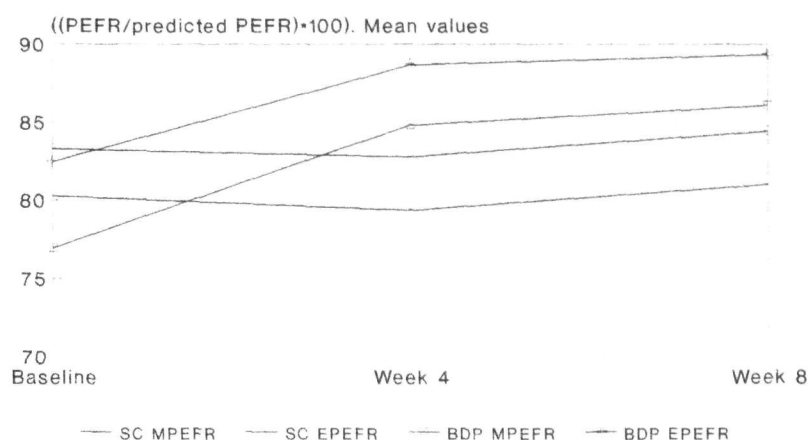


Fig. 1. Morning and evening peak flow throughout 8-week treatment period for SC group ($n = 19$) and BDP group ($n = 18$).

Symptom score

Night and day. There were significant decreases in severity of all symptoms during both night and day in both treatment groups (asthma symptoms, tightness, and cough: $P < 0.001$). Thus, the reduction of symptoms appeared to be the same in both the SC and the BDP groups.

Additional daytime bronchodilator medication. The reduction in rescue medication did not differ significantly between the SC and the BDP groups ($P = 0.55$). In the SC group, a 62% reduction was found (from 3.8 to 1.4 puffs daily), and in the BDP group a 56% reduction (from 3.3 to 1.4 puffs daily). The decrease in bronchodilator use from base line to the end of the treatment period was highly significant for both groups ($P < 0.01$) (Fig. 2).

Clinical lung function: FEV_1 . In the run-in period, two FEV_1 measurements were taken (at the start and at the end of the 2-week run-in period), and the mean of those two measurements was used for calculations. During treatment, there was a significant improvement of FEV_1 in both groups. In the SC group,

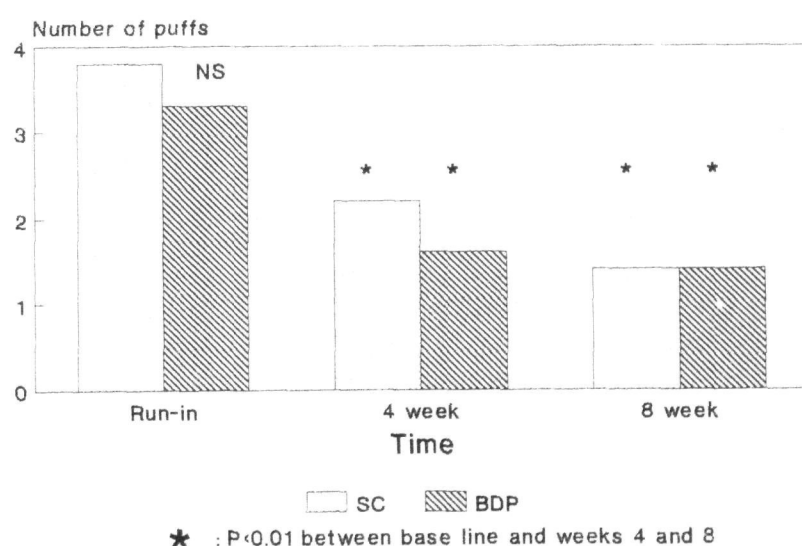


Fig. 2. Daytime rescue medication. Mean values. SC $n = 19$ and BDP $n = 18$.

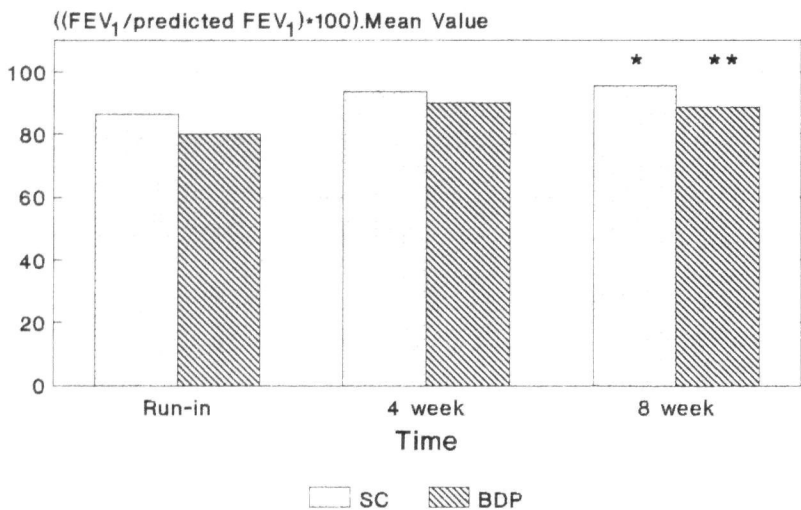


Fig. 3. FEV₁ in relative values: SC (n = 19) and BDP (n = 18) groups. * Difference from base line to week 8: P = 0.003; ** difference from base line to week 8: P = 0.001.

FEV₁ improved significantly, showing 0.29 l or 9.19% over the 8-week period (P = 0.003 ((95% CI = 3.41, 15.05)). In the BDP group, FEV₁ improved significantly, showing 0.28 l or 8.40% over the 8-week period (P = 0.001 ((95% CI = 3.90, 12.91)). The difference between the two groups in relative FEV₁ values in the run-in period was not statistically significant ((P = 0.38 (95% CI = -7.61, 19.10)), and at the end of the 8-week treatment period, the difference was still not statistically significant ((P = 0.38 (95% CI = -22.82, 9.26)) (Fig. 3).

Physicians' and patients' assessment of efficacy. There was an equal preference for the two treatment groups by patients and investigators, with no significant difference between the two treatments (Table 2).

Safety. During the study, a total of eight patients reported a total of 11 adverse events (six in the SC group and five in the BDP group). The events are summarized in Table 3. No major events appeared in any of the groups.

Table 2. Patients' and physicians' opinions of efficacy

Effectiveness	Score	No. of patients		No. of clinicians	
		SC	BDP	SC	BDP
High	1	11	9	5	10
Moderate	2	3	5	8	4
Slight	3	3	1	4	1
None	4	1	1	1	1
Worsening	5	0	0	0	0
Missing data		1	2	1	2
Total no.		19	18	19	18
Mann-Whitney U-test					
P value		0.9862		0.0845	

SC: sodium cromoglycate; BDP: beclomethsone dipropionate.

Table 3. Adverse events reported during treatment period

Adverse event	SC	BDP
Bad taste	1	1
Dry mouth	0	1
Dry throat	1	1
Fever	1	0
Nausea	1	1
Pneumonia	0	1
Rash	1	0
Tachycardia	1	0
No. of events	6	5
No. of patients reporting at least one event	4	4

SC: sodium cromoglycate; BDP: beclomethsone dipropionate.

Laboratory data

There were no laboratory assessments during the trial.

Discussion

It is now generally agreed that anti-inflammatory drugs should be introduced early in the treatment of asthma (1, 16). Inhaled corticosteroids and inhaled SC are anti-inflammatory. The mode of action of steroids is still uncertain, but they do act on various components of the inflammatory response in asthma; for instance, reducing the number of inflammatory cells; reducing the vascular leakage caused by inflammatory mediators in the airway; and, when given on a long-term basis, reducing bronchial hyperresponsiveness. Side-effects are uncommon when low doses of steroid (< 400 µg daily) are given by inhalation (1). Side-effects are dose-dependent, and it has been shown that important systemic side-effects appear with doses over 1500 µg (3, 12). The mode of action of SC is still unknown. When inhaled, it inhibits the immediate response to allergen and exercise, possibly by inhibiting the release of mediators from mast cells (5, 14). SC also prevents late-response and bronchial hyperresponsiveness, possibly by acting on other inflammatory cells, such as macrophages or eosinophils. The duration of the treatment period seems to be an important factor in the efficacy of SC on bronchial hyperresponsiveness, 8–12 weeks being a minimum (11). Side-effects with inhaled SC, especially when given by MDI, are extremely rare; the drug is well tolerated (1).

There have been few comparative trials undertaken between these two compounds in adults, and, to date, none between the higher-dose aerosol formulation of SC and standard inhaled BDP. To date, published trials with the 5-mg aerosol of inhaled SC have been placebo controlled (4, 17). Previous comparative trials have compared Spincap® formulations (powder) of SC with BDP, and they have been

conducted primarily in children (6, 7, 9, 10, 13, 15). In one study, SC (MDI) 8 mg daily was compared with BDP (MDI) 400 µg daily in 38 younger adult patients with atopic asthma (18).

When either inhaled BDP at a dose of 400 µg/d or inhaled SC at a dose of 40 mg/d was added to a base-line treatment of inhaled β_2 -agonist, all patients exhibited a reduction in asthma severity. In both groups, an improvement of the morning and evening diary PEFR was observed; this was statistically insignificant for the SC group but significant for the morning PEFR in the BDP group. The increase took place mainly within the first 4-week period for the BDP group, while the slight increase in PEFR for the SC group took place after 8 weeks of treatment. A significant improvement of the FEV₁ was observed for both groups. In symptom scores, both groups were equally effective. In addition, both groups showed a highly significant reduction in the need for daily use of inhaled rescue medication: 62% for the SC group and 56% for the BDP group. The improvements in asthma control and severity were reflected in the global opinion, too, with over 70% of both treatment groups reporting the treatment to be very or moderately effective.

Theoretically, the improvement with time could be a regression toward the mean effect, but because it previously has been shown that both SC and BDP are effective antiasthmatic drugs, as compared with placebo, it might be justified from this study to conclude that both drugs are effective in the treatment of asthma.

These results support the early use of anti-inflammatory drugs in the management of asthma to achieve better symptom control, improved pulmonary function, and reduced need for traditional bronchodilators.

In conclusion, this trial shows that inhaled BDP 400 µg/d and inhaled SC 40 mg/d show equal efficacy in pulmonary function, symptom scores, reduction of rescue medication, and patients' and clinicians' opinion of the treatment in adults with bronchial asthma.

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