

Inhibition of exercise-induced-asthma (EIA) by nedocromil sodium and sodium cromoglycate in children

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Nedocromil sodium (Ned) 4 mg, sodium cromoglycate (SCG) 10 mg, and placebo were compared for their efficacy in preventing exercise-induced asthma. Nineteen asthmatic children aged six to 15 years performed a treadmill exercise test before and 20' after a single dose of drug in a double-blind trial. Both active drugs performed significantly better than placebo; in fact the exercise challenge resulted in a mean maximum fall in FEV1 of $26.1 \pm 14.9\%$ after placebo, but only of $14.6 \pm 11.5\%$ after SCG ($P < 0.05$), and $11.0 \pm 12.4\%$ after Ned ($p < 0.01$). Measurements of PEFR gave similar results, while the effect of treatment on FEF 25–75 was significant for Ned alone ($p < 0.05$). Direct comparison between Ned and SCG at different time points demonstrated significant differences in FEV1 at 1 min ($p < 0.05$) with a better overall performance of Ned. In individual patients, complete protection was provided in 9 patients with SCG, in 14 patients with Ned and in 2 with placebo. No side effects were observed. This study suggests that at the dosages used there are only slight differences between SCG and Ned activity in the prevention of exercise-induced asthma.

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Nedocromil sodium (Ned) is a new non-bronchodilator, non-steroidal antiasthmatic agent that displays similar properties to sodium cromoglycate (SCG), and in addition exhibits a preferential activity in stabilizing mucosal mast cells (1).

In ascaris-sensitized macaque monkeys, Ned exhibited an effect *in vitro* on histamine, leukotriene C4 and prostaglandin D2 release from lavaged mast cells (2), whereas SCG gave little or no effect. It has been shown that Ned (4 mg) is more potent than SCG (10–12 mg) via metered dose inhaler in inhibiting immediate bronchoconstriction provoked by challenges with fog (3) and sulphur dioxide (4). The efficacy of Ned in the treatment of clinical asthma has been demonstrated in open and double-blind studies (5, 6). Sodium cromoglycate was first used in 1968 (7) to prevent EIA and other investigators have subsequently confirmed this effect (8).

At present only a few studies, all performed in adults, have compared the effect of Ned and SCG on EIA (9–10). These studies conclude that at the

recommended doses both drugs are equally effective in preventing EIA.

The greater protective effect of Ned demonstrated in different experimental models (1–4), and the need to know whether or not Ned offers any advantage over SCG, induced us to perform a trial investigating the effect of SCG as compared to Ned in EIA in children.

Material and methods

Nineteen children (13 boys and 6 girls aged 6 to 15 years) with asthma and EIA were studied. Informed consent was obtained from both children and parents. All patients had perennial episodes of airway obstruction which could be relieved by antiasthmatic drugs. All used inhaled beta-2 agonists. Additional drugs used in the previous six months were SCG (6 children), theophylline (3 children) and beclomethasone (2 children). Based on skin prick tests to 12 common allergens, they were all

Table 1. Maximum percentage decrease in FEV1, PEFR, and FEF 25-75 (mean $\pm$ SD) after placebo, SCG, and Ned in 19 patients

	FEV1	PEFR	FEF 25-75
No medication	28.7 ($\pm$ 13.3)	22.2 ($\pm$ 17.0)	42.2 ($\pm$ 24.0)
Placebo	26.1 ($\pm$ 14.9)	19.5 ($\pm$ 16.9)	37.7 ($\pm$ 21.8)
SCG	14.6 ($\pm$ 11.5)	11.6 ($\pm$ 10.0)	29.5 ($\pm$ 23.8)
Ned	11.0 ($\pm$ 12.4)	9.1 ($\pm$ 10.9)	22.0 ($\pm$ 25.4)
SCG vs pl	$p < 0.05$	$p < 0.05$	$p = n.s.$
Ned vs pl	$p < 0.01$	$p < 0.05$	$p < 0.05$
SCG vs Ned	$p = n.s.$	$p = n.s.$	$p = n.s.$

considered atopic. Fifteen were allergic to house dust mite, 6 to pollens, 4 to animal dander and 2 to microfungi.

Pulmonary function testing

Pulmonary function was monitored with a pneumotachograph (Cosmed Italy) and forced-expiratory-volume in 1 second (FEV1), peak expiratory flow rate (PEFR), and forced expiratory flow between the middle half of forced vital capacity (FEF 25-75) were measured. Predicted normal values for spirometry were obtained from Zapletal et al. (11). The presence of EIA was demonstrated by a fall of at least 15% in FEV1 after the exercise test.

Trial design

The patients attended an initial screening having abstained bronchodilators and long acting inhaled beta-2 agonists for at least 12 hours, and from short-acting inhaled bronchodilators for at least 6 hours. Patients who had been treated with SCG or inhaled steroids in the previous month were excluded. None of the subjects had had respiratory infections within 3 weeks of the trial.

Each child ran on a treadmill for 6 min with slope and speed adjusted to give an increase in pulse rate to 170-180 beats/min. The temperature in the laboratory throughout the study was between 20-22°C and the relative humidity ranged between 45% and 50%. In a double-blind placebo-controlled study, each patient was tested on three treatment regimens in random order on three separate days: a) Ned (2 mg/puff): 2 puffs; b) SCG (5 mg/puff): 2 puffs; c) placebo (propellant only): 2 puffs.

The two inhalations were given in successive breaths or as close as convenient by a trained technician or a physician using a spacer (Volumatic-Glaxo) to optimize compliance. The three treatments were given on separate days and patients were again instructed to abstain from medication.

Lung function measurements (FEV1, PEFR, and FEF 25-75) were taken before drug adminis-

tration, before the exercise test (20 min after the drug administration) and then 1 min - 5 min - 10 min - 15 min - 20 min after the exercise. The mean of the two readings taken prior to the challenge was used as the baseline for comparison.

The bronchial responses to exercise were expressed as maximum percentage fall in FEV1, PEFR, and FEF 25-75 from the pre-exercise baseline values:

$$\frac{\text{pre-exercise baseline value} - \text{lowest postexercise value}}{\text{pre-exercise baseline values}} \times 100\%$$

The percentage fall in FEV1 at different times after treatments was also calculated. Complete protection was considered to be obtained if the % of fall in FEV1 after treatment was within the normal range (<15%).

Statistics

The results were analyzed with student's t-test, differences were considered significant if $p < 0.05$.

Results

The mean predrug baseline FEV1 was 2.22 L, 2.23 L, and 2.17 L for placebo, CGS, and Ned, respectively, and there were no statistically significant differences among these values. The patients were either slightly or not at all obstructed, since these baseline values were 94.5%, 94.3%, and 92.4% of the predicted normal values.

Both active drugs were significantly more protective than placebo; in fact, the exercise challenge resulted in a mean maximum fall in FEV1 of $26.2 \pm 14.9\%$ after placebo, but of only $14.6 \pm 11.5\%$ after SCG ($p < 0.05$) and $11.0 \pm 12.4\%$ after Ned ($p < 0.01$). PEFR measurements gave similar results, while the effect of treatment on FEF 25-75 was significant for Ned alone ($p < 0.05$) (Table 1).

In individual patients, complete protection was provided in 9 patients with SCG, in 14 patients with Ned and in 2 patients with placebo (Table 2). Eight of nine patients who received protection

Table 2. Individual patient protection (number of patients) in 19 children performing treadmill exercise challenges after a single dose of medication

	Complete protection*	No protection
SCG	9	10
Ned	14	5
Placebo	2	17

* Complete protection equals percent of fall in FEV1 within normal range

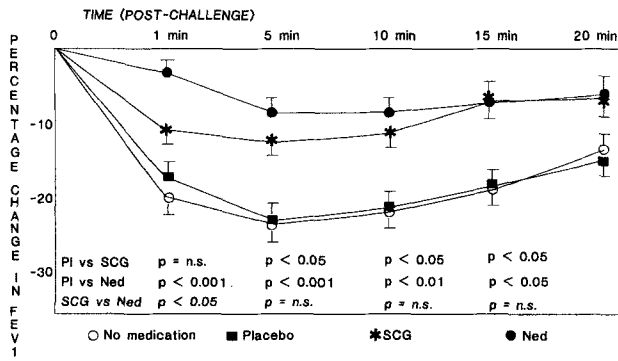


Fig. 1. Percent of fall in FEV1 (mean and SE) and significance at different time points in 19 children performing treadmill exercise challenge after a single dose of medication.

from EIA with SCG were also protected with nedocromil sodium, while 5 patients received complete protection with Ned but not with SCG.

After the exercise challenge, the percent fall in FEV1 was significantly lower than placebo for Ned at all time points (1 min – 5 min – 10 min – 15 min – 20 min), and for SCG at all time points except 1 min. A comparison between Ned and SCG at different time points showed a statistically significant difference ($p < 0.05$) only at 1 min (Fig. 1). Four children complained of an unpleasant taste after Ned inhalation, and 2 after SCG. These side effects were however mild.

Discussion

Nedocromil sodium is a new drug of proven efficacy in the treatment of asthma, and in many *in vivo* and *in vitro* studies this drug has demonstrated its superiority over SCG (1–4). Exercise-induced asthma has been used as a provocation test for a number of years to assess the relative efficacy and duration of the action of different drugs (12). In these studies (13–15), beta-2 agonists by inhalation were the most effective for preventing EIA, while oral theophylline, inhaled SCG and ipratropium bromide were less effective and not significantly different. Moreover, Ned has

been shown to display a significant protection in adults (9, 10), children (16–18) and adolescents (19). The duration of action of Ned and SCG seems to be similar, with SCG possibly having a somewhat longer effect (9).

In our study patients performed the treadmill exercise only once after drug administration, and we therefore had no information about the duration of effect of the two drugs. We have here demonstrated a significant effect of both Ned and SCG vs placebo in preventing EIA. Analyzing the maximum percent decrease in spirometric parameters, only Ned demonstrated significant protective effect on FEF 25–75. This spirometric parameter evaluates abnormalities in small airways, and the relative inefficacy of SCG in preventing small airway involvement during EIA has already been reported (15). On the other hand, König et al. (9) found that 2 h after drug administration the percent fall in FEF 25–75 was 23.4 ± 13.7 with SCG and 32.5 ± 17.4 with Ned. The activity of the two drugs on small airways is therefore controversial.

Direct comparison between the two drugs showed that Ned has a more rapid action than SCG and a more pronounced protective effect (Fig. 1). The protection in individual patients showed some differences (Table 2); complete protection was provided by Ned in 14/19 (73.6%) patients, and by SCG in 9/19 (47.3) patients. These values are in partial agreement with those reported by others (9, 10).

Previous investigators have demonstrated that different doses of Ned given by pressurized aerosol (20) and different doses of SCG in powder (21) or from a metered dose inhaler (22) have the same effect in preventing EIA. However, there is a lack of real dose-response studies. In the present study we compared Ned 4 mg and SCG 10 mg inhaled from metered dose inhalers and it can not be excluded that the difference in activity found is mainly due to the different dosage. The protective effect of the two drugs varied in individuals; there was a subgroup of 4 children who were unrespon-

Table 3. Percent of fall in FEV1 (mean $\pm$ SD) and significance at different time points in 19 children performing treadmill exercise challenge after a single dose of medication

	Time (post-challenge)				
	1'	5'	10'	15'	20'
No medication	19.5 ($\pm$ 13.8)	23.1 ($\pm$ 13.4)	21.6 ($\pm$ 12.1)	18.5 ($\pm$ 14.4)	13.2 ($\pm$ 13.0)
Placebo	16.9 ($\pm$ 14.4)	22.6 ($\pm$ 13.6)	21.0 ($\pm$ 14.7)	18.0 ($\pm$ 14.8)	14.6 ($\pm$ 12.1)
SCG	10.6 ($\pm$ 12.9)	12.2 ($\pm$ 10.6)	11.1 ($\pm$ 10.4)	6.8 ($\pm$ 10.7)	6.5 ($\pm$ 10.7)
Ned	3.1 ($\pm$ 7.0)	8.4 ($\pm$ 9.1)	8.3 ($\pm$ 10.8)	7.0 ($\pm$ 10.6)	6.0 ($\pm$ 10.3)
PI vs SCG	$p = \text{n.s.}$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
PI vs Ned	$p < 0.001$	$p < 0.001$	$p < 0.01$	$p < 0.05$	$p < 0.05$
SCG vs Ned	$p < 0.05$	$p = \text{n.s.}$	$p = \text{n.s.}$	$p = \text{n.s.}$	$p = \text{n.s.}$

sive to both Ned and SCG, while in 5 cases children responded to Ned and not to SCG. Again, there was evidence of a placebo effect in 2 children.

This is the first comparison of SCG and Ned in preventing EIA in children. Both these drugs demonstrated a positive clinical effect, and it is premature to say whether the more frequent, rapid and pronounced preventive effect of Ned is sufficient to warrant a preference for this drug in clinical practice. Other studies investigating the efficacy and duration of effect of these two drugs are thus required.

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