

A comparative study of the effects of two different doses of nedocromil sodium and placebo given by pressurised aerosol in exercise-induced bronchoconstriction

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Fourteen adult subjects with stable asthma were treated using a double-blind crossover, randomised protocol, with either nedocromil sodium (4 mg or 2 mg) or placebo. The agents were administered from matched pressurised aerosol inhalers 30 min before exposure to an exercise regimen which, on a previous screening day, resulted in a 24-53% (mean: 33.9%) decrease in peak expiratory flow (PEF). Both doses of nedocromil sodium were significantly superior to placebo in preventing the exercise-induced decrease in PEF and were without side effects. This study confirms and extends the results of earlier trials with nedocromil sodium and further supports the contention that this new agent may be of benefit in the treatment of reversible obstructive airways disease in the adult patient.

Key words: asthma; drug evaluation; nedocromil sodium; quinolines; therapeutic use; respiratory therapy.

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There is considerable evidence that reversible obstructive airways disease has several pathophysiological components (11). One component which appears to underlie the development of inflammation and bronchial hyperreactivity in asthmatic patients is the release of mediators from mast cells in the lung (8, 9). Animal studies have shown the existence of at least 2 mast cell sub-types, connective tissue and mucosal mast cells, and a similar functional mast cell heterogeneity is thought to occur in man (10, 15). Some years ago, the introduction of the mast cell stabilising agent sodium cromoglycate represented an important therapeutic advance; however, sodium cromoglycate is known to be more effective in stabilising connective tissue mast cells than mucosal mast cells. The continued search for agents having enhanced effects on mucosal mast cells, and the inflammatory aspects of airways disease, has

identified a new compound, nedocromil sodium (Tilade®, Fisons plc.), which has a wider spectrum of activity in animal models of asthma (7, 14) and has been found effective in bronchial provocation tests (2, 3, 16-19) and in the treatment of chronic asthma (3, 13).

The present study was designed to compare the efficacy of aerosolised nedocromil sodium at 2 dose levels with the effect of placebo on exercise-induced bronchoconstriction (EIB) in adult asthmatic patients.

MATERIAL AND METHODS

Fourteen patients, 6 males and 8 non-pregnant females aged 21 to 49 years, took part in the trial. All had asthma and reproducible EIB with a post-exercise fall in PEF of > 20%. Patient characteristics are detailed in Table 1. Prior to the study period theophylline usage was suspended for 24 h

and β_2 -bronchodilators for at least 12 h. Oral corticosteroids had not been taken for 3 months, with the exception of patient No. 2, who demonstrated consistent EIB while continuing routine oral prednisolone therapy. Inhaled steroids were taken as usual during the trial.

Exercise challenge, established for each patient on a pre-study screening day under the same conditions of treatment, consisted of 6 min treadmill running under controlled conditions of temperature (23°C) and humidity (45%). Speed was adjusted individually to give a fall in PEF of 20–50%. Tests were then performed at the same time of day, and on consecutive days as far as possible (within a week in 12 cases, and 2 weeks overall). Baseline measurements of PEF were taken 10 and 5 min prior to treatment, and the test was continued only if ventilatory function was within 15% of the predicted normal value. PEF was recorded as the maximum of 3 readings throughout.

Test procedure involved inhalation of 2 puffs from pressurised aerosol cans of identical appearance, holding the breath for at least 5 s after each inhalation, and allowing no longer than 30 s between puffs. PEF was recorded after 5, 10, 20, and 25 min, and exercise chal-

lenge performed 30 min after test treatment. Following challenge, lung function was monitored at regular intervals for 30 min, when the procedure was terminated by use of an aerosol bronchodilator. The bronchodilator was used to arrest EIB before the 30-min end-point if a steady low value of PEF had already been reached. For each treatment day, the greatest recorded fall in PEF was used in the analysis.

Treatments were assigned randomly on a double-blind/crossover basis and comprised 1 mg or 2 mg per actuation of nedocromil sodium, or placebo. Patients' informed consent to the trial was obtained in all cases, and the procedures were in accordance with the Helsinki Declaration of 1975 and had the approval of the hospital Ethics Committee.

Statistical assessment of the effects of test treatments on EIB was carried out at the 5% level using a repeated measures analysis of variance and Duncan's multiple range test.

RESULTS

There were no significant changes in the mean pre-treatment PEF measurement (407 l/min at initial screening) on any of the 3 study days. All

Table 1

Patient characteristics at admission

Subject No.	Age (years)	Sex	Weight (kg)	Height (cm)	Asthma duration (years)	Current therapy
1	29	F	92	175	3	theo po, β_2 + inh
2	44	F	65	165	5	theo po, steroid po + inh
3	31	F	61	168	25 +	steroid inh
4	49	M	83	179	32	steroid inh, β_2 inh
5	21	M	60	163	15	theo po, steroid inh, β_2 inh
6	24	F	58	164	13	theo po, steroid inh, β_2 po
7	33	M	60	168	?	theo po, steroid inh, β_2 inh
8	24	F	64	164	19 +	steroid inh, β_2 inh
9	26	M	71	174	21 +	steroid inh, β_2 inh
10	32	F	64	168	8	steroid inh
11	22	M	81	182	4	steroid inh, β_2 inh
12	41	M	78	178	12	β_2 inh
13	31	F	59	180	25 +	β_2 inh
14	25	F	75	180	8	β_2 inh
Mean $\pm$ SEM	31 $\pm$ 2		69 $\pm$ 3	172 $\pm$ 2		

theo = theophylline, β_2 = β_2 bronchodilator, po = oral, inh = inhaled

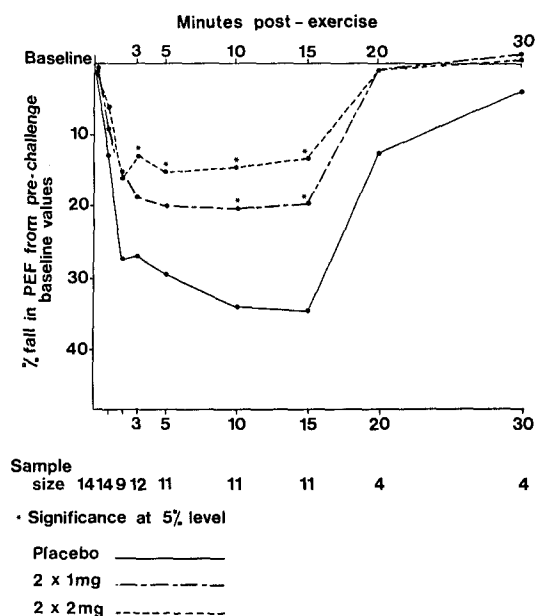


Fig. 1. Percentage decrease in PEF after exercise challenge in asthmatic patients pre-treated with aerosolised placebo (—) or nedocromil sodium 2 x 1 mg (— · —) or 2 x 2 mg (----).

3 treatment groups showed small increases (approximately 5%) in PEF between treatment and the start of exercise challenge, with no difference between groups.

Fig. 1 shows the time course for the fall in PEF from the pre-challenge baseline following exercise challenge in the 3 treatment groups. The maximum percentage decrease in PEF in the placebo-treated group (41.3%) was significantly ($P < 0.001$) reduced following treatment with either 2 mg (25.9%) or 4 mg (21.3%) nedocromil sodium, with no significant difference between the dose levels of the drug. Paired comparisons at the 5% level showed significant differences between nedocromil sodium 2 mg and placebo at 10 and 15 min after challenge, and between nedocromil sodium 4 mg and placebo at 3, 5, 10 and 15 min after challenge. Although there were no statistically significant differences between the 2 dose levels of nedocromil sodium, the higher dose gave better protection (Fig. 1).

A bronchodilator was used to reverse EIB after no more than 15 min in 8 patients follow-

ing placebo treatment, in 5 patients after nedocromil sodium 2 mg, and in only 2 patients after nedocromil sodium 4 mg.

No adverse effects were reported. Unusual reactions were minor and subjective, and included coughing (2 patients all treatments), and dry (1 patient, placebo) or itching throat (1 patient, 4 mg nedocromil sodium) following inhalation of both nedocromil sodium and placebo. Five patients commented on the taste after nedocromil sodium, and 1 after placebo inhalation.

DISCUSSION

The results of this study are in accord with other reports (16, 18) and confirm that pretreatment with single doses of nedocromil sodium aerosol inhibits EIB. Deterioration of lung function following exercise is a consequence of airways hyperreactivity and occurs in the majority of asthmatic patients (4). The degree of non-specific bronchial hyperreactivity is a measurer of the severity of disease (12) and has been linked with the inflammatory components of asthma (5).

Early therapeutic studies (6, 13) with nedocromil sodium have shown the drug to be effective in the treatment of asthma in adult patients and, when given in regular dosage, it was found to reduce seasonal non-specific bronchial hyperreactivity in adult atopic rhinitic subjects (1). Additional single-dose studies have indicated the effectiveness of nedocromil sodium in alleviating bronchoconstriction induced by allergen (19), sulphur dioxide (2), adenosine (3) and fog (17), thus confirming the protective action of this compound in the hyperresponsive airways of asthmatics.

The mode of action of nedocromil sodium and its place in the long-term management of asthma remain to be fully evaluated. On the basis of the results presented here it is concluded that pretreatment with 2 mg and 4 mg nedocromil sodium aerosol is effective in the attenuation of EIB in adult asthmatic patients. It is suggested that the drug merits further investigation as an agent for the treatment of reversible obstructive airways disease.

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