

A double-blind, placebo-controlled study to assess the efficacy of nedocromil sodium in the management of childhood grass-pollen asthma

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Summary

The aim of this double-blind placebo-controlled trial was to assess the efficacy and tolerance of nedocromil sodium at a dose of 4 mg four times daily, in the management of children suffering from grass-pollen asthma. Thirty-one children suffering from seasonal asthma (24 boys and seven girls, aged 4–21 yr, mean 11 yr) were enrolled in the study during the 1988 pollen season. Only one child was aged 4 yr, and she was a cooperative girl able to use the metered dose inhaler properly. In addition, in each group there was a patient aged 20 and 21 years, respectively, who had been followed up by us since childhood. Treatments were delivered by pressurized aerosol over a period of 4 weeks following a 1-week baseline, during which patients were required to show active disease by obtaining a minimum symptom score (almost 2 points of severity score on at least 3 days of the baseline period). The patients were randomly assigned to both treatment groups, all were taking inhaled or oral bronchodilators, when necessary. Twenty-nine patients completed the trial, 16 in the nedocromil sodium treatment group and 13 in the placebo group. One child of each group was withdrawn due to treatment failure.

Statistically significant differences in favour of nedocromil sodium were found regarding morning tightness and mean morning PEFR values on diary cards ($P < 0.01$ and $P < 0.05$, respectively), bronchodilator usage ($P < 0.05$), pulmonary function tests (PFT) at clinic visits ($P < 0.05$), and in parents' opinion ($P < 0.05$). No differences between the two treatments were recorded in terms of severity of asthma in the baseline period and, in addition, of cough, day/night-time asthma and mean evening PEFR values on diary cards after 2 and 4 weeks of both treatments. Eight patients, four from both treatment groups, reported mild unusual symptoms such as headache, sore and aching throat, and abdominal pain. No evidence of any treatment effects were found in laboratory tests. We conclude that nedocromil sodium is indicated in the first-line treatment of children with bronchial asthma, in addition to being well tolerated at the dose of 4 mg four times a day.

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Introduction

Nedocromil, the disodium salt of a pyranoquinoline-dicarboxylic acid, is a new anti-allergic (anti-asthmatic) and anti-inflammatory agent which inhibits the activation and mediator release from mast-cells, neutrophils, eosinophils, macrophages, monocytes and platelets [1]. In particular, it shows a selective 'mucosal' mast-cell stabilizing property (at least 100 times greater in potency than

sodium cromoglycate) (SCG) [1]. In asthmatic adults it has been shown to inhibit the bronchoconstriction induced by bronchial challenge with antigen, exercise, adenosine, sulphur dioxide, distilled water, and cold air [1–6]. In controlled clinical trials, nedocromil sodium has been found to reduce the severity of asthmatic symptoms and the use of both bronchodilator and corticosteroid drugs in perennial asthmatic adults, with excellent tolerability [7–15]. In addition, it has been shown to decrease

the bronchial reactivity during the pollen season in adults with grass-pollen rhinitis [16]. In controlled studies in children, nedocromil sodium has been demonstrated to protect against exercise-induced asthma [17–21], but we lack data about its efficacy and tolerance in childhood asthma. The present study aims to extend knowledge of the drug into a paediatric population using the dosage of 4 mg four times daily.

Patients and methods

Patients

Thirty-one patients suffering from seasonal asthma (24 boys and seven girls, aged 4–21 yr, mean 11 yr) entered into the study during the 1988 pollen season. Only one child was aged 4 yr, and she was a cooperative girl able to use the metered dose inhaler properly. In addition, in each group there was a patient aged 20 and 21 years, respectively, who had been followed up by us since childhood. They were out-patients attending (for the first time or for re-assessment) the Allergy and Clinical Immunology Division of the Department of Paediatrics of the University of Roma 'La Sapienza' Medical School. All the patients suffered from seasonal asthma, had positive skin test and/or RAST to grasses, and were symptom-free during the rest of the year. The study was approved by the Ethical Committee. All parents and the 20- and 21-yr-old patients gave their informed consent.

Study design

All patients were enrolled in the study during the first week of May 1988. They lived in Rome city, where the grass-pollen season starts at the beginning of March and continues until the end of June. When the patients were enrolled, the mean daily grass-pollen count was 85 grains/mq³ of air, increasing to 110 grains/mq³ during the month of May and the first week of June when the study was done.

The study design was double-blind placebo-controlled. The inclusion criterion for enrolment in the study was that the patients had to be suffering from seasonal asthma. Diagnosis was based on a positive history, positive skin tests and/or specific IgE to grass-pollen, and confirmed by at least 15% reversibility to airway obstruction in response to a bronchodilator aerosol. Treatments were delivered by metered dose pressurized aerosol delivering either 2 mg of nedocromil sodium per actuation, or matching placebo. The dosage was two inhalations four times daily. All patients were trained by one of us (A.D.F.) to use the metered dose inhaler correctly. In

addition, their parents were instructed to supervise the procedure.

On entry all patients were taking inhaled or oral β -2 adrenergic drugs (salbutamol) when needed. The nebulizer (Nebula, Markos, Monza, Italy) aerosol employed by all patients atomized a 2-ml solution in 7 min delivering particles ranging from 0.5 to 5 μ m. If the asthma worsened they used oral theophylline and, if necessary, betamethasone. Patients who had a respiratory infection in the previous 6 weeks or received medication with SCG, ketotifen and oral/inhaled corticosteroids in the 4 weeks before the baseline period were excluded. The use of such medications and of oral antihistamine preparations were not permitted during both baseline and treatment periods. The trial was designed to cover a 5-week period, consisting of a 1-week baseline period followed by a 4-week period of one of the trial treatments, randomly allocated according to a code sheet. Patients were required to have recorded during the baseline period a minimum score of symptom severity (almost 2 points scored on at least 3 days of the baseline period) and the need to use salbutamol (almost one inhalation, four times on these days).

The patients were seen at the beginning and the end of the baseline period, and after the 2 and 4 weeks of the trial. At the first visit, clinicians provided information on patients and their asthma and performed a detailed physical examination. The severity of asthma was assessed on a 0–4 scale (0=no symptoms, 1=mild, 2=moderate, 3=severe, 4=very severe), and pulmonary function tests (FVC, FEV₁ and PEF_R) were performed by a Vitalograph spirometer (Vitalograph Ltd, London, U.K.). Reversibility of airway obstruction was measured if not available, and all medications being taken by the patients were listed. In addition, parents were instructed to keep a daily diary card throughout the trial on which they should record symptom scores for morning tightness, day/night-time asthma and cough, using a 0–4 scale (0=no symptoms, 4=very severe), the use of permitted medications, and the values of morning and evening PEF_R, using a mini-Wright (Airmed Ltd, London, U.K.) peak flow meter (best of three maximal attempts on each occasion). At each visit, both the severity of asthma and pulmonary function tests were assessed, and parents were asked about the 'unusual symptoms' recorded. The nature, timing and severity of these symptoms were recorded and assessed as probably, possibly, or unlikely to be due to the trial treatment. At the end of the trial, parents were asked to assess the efficacy of the treatment using a 1–5 scale (1=very effective, 2=moderately effective, 3=slightly effective, 4=no effect, 5=made condition worse). A record was kept of all patients withdrawn due to worsening of their asthma. Blood and

pulse rates were checked at each visit. Blood and urine samples were taken for routine laboratory monitoring (blood count, liver function tests, azotemia, and glycaemia) at the beginning and end of the study period.

Statistical analysis

Pulmonary function tests were analysed comparing baseline measurements and were recorded during and at the end of the treatment period. A parametric test (Student's *t*-test for paired data or analysis of variance) was used. All other variables were analysed using non-parametric methods. Comparisons with the baseline period was made with Wilcoxon matched pairs signed ranks. Statistical hypothesis testing of treatment effects was based on a significance level of 0.05 using two-tailed probabilities.

Results

Twenty-nine patients completed the trial, 16 receiving nedocromil sodium and 13 receiving placebo. Both groups were similar with respect to age, height, severity of asthma, and duration or type, but not with respect to sex: nedocromil sodium group consisted of 15 boys and one girl and placebo group of eight boys and five girls (Table 1).

One child from each treatment group was withdrawn requiring oral steroids because of a worsening of their asthma.

Clinical assessment

On entry to the trial both treatment groups were similar in severity of asthmatic symptoms recorded on diary cards during the baseline period (1 week) and in pulmonary function tests (FCV, FEV₁ and PEF_R). Pulmonary function tests measured at each visit during the treatment period improved with a statistically significant difference in favour of the nedocromil sodium group (FCV: $P < 0.01$; FEV₁: $P < 0.05$; and PEF_R: $P < 0.05$, respectively) (Fig. 1). As regards the severity of patients' asthma, we did not find a significant difference in response to the allocated treatment between the two groups, although the trend favoured the nedocromil sodium group.

Diary cards

The analysis of patients' asthmatic symptoms scores and mean PEF_R values recorded at home on diary cards showed a statistically significant difference in favour of nedocromil sodium group at the end of the trial (week 4) for the day/night-time asthma ($P < 0.01$). In children taking the active drug the improvement was accompanied by a significant reduction in inhaled bronchodilator usage

Table 1. Characteristics of the 29 patients who completed the trial

	Nedocromil sodium	Placebo
Numbers	16	13
Boys	15	8
Girls	1	5
Age (yr)		
Range	4-21	6-20
Mean	11.8	10.5
Height (m)		
Range	0.98-1.83	1.18-1.80
Mean	1.448	1.415
Severity of asthma		
Mild	3	3
Moderate	9	6
Severe	4	4
FVC (l)		
Range	1.60-3.20	1.18-3.35
Mean	2.25	2.15
FEV ₁ (l)		
Range	1.32-2.72	1.15-2.55
Mean	1.93	1.77
PEFR (l/min)		
Range	100-510	160-510
Mean	275	261.9
Medication on entry		
Inhaled bronchodilators	16	11
Oral bronchodilators	7	6

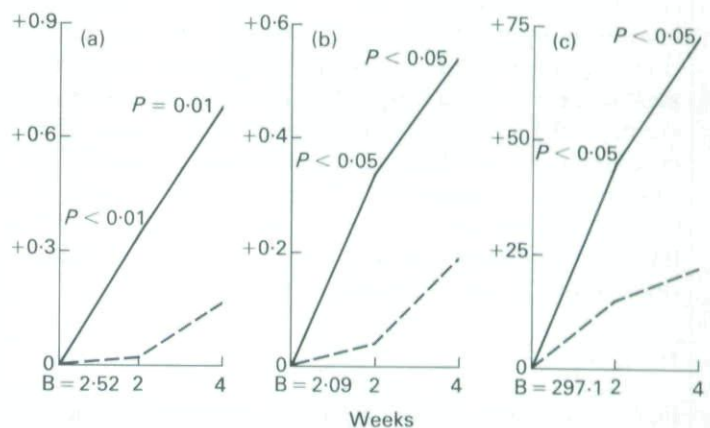


Fig. 1. Changes in (a) FVC, (b) FEV₁ and (c) PEF_R recorded at clinic visits between baseline and weeks 2-4 of treatment period. B, baseline; (—) nedocromil sodium; (---) placebo.

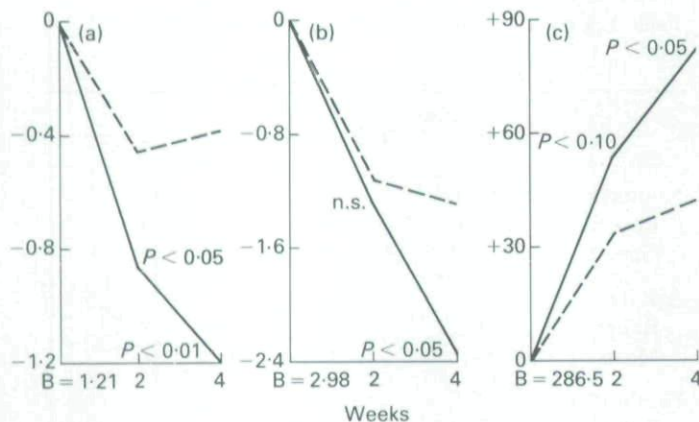


Fig. 2. Changes in mean severity scores of (a) morning tightness, (b) bronchodilator usage, and (c) morning PEFR recorded on diary cards between baseline and weeks 2–4 of treatment period. B, baseline; (—) nedocromil sodium; (---) placebo.

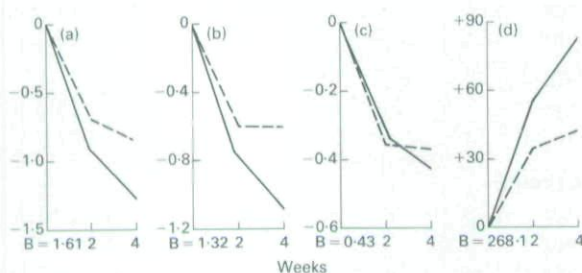


Fig. 3. Changes in mean severity scores of (a) cough, (b) day-time asthma, (c) night-time asthma and (d) evening PEFR recorded on diary cards between baseline and weeks 2–4 of treatment period. B, baseline; (—) nedocromil sodium; (---) placebo.

($P < 0.05$) from week 4, and a significant improvement in mean morning PEFR values ($P < 0.05$) from week 2 (Fig. 2). However, no statistically significant improvement was recorded on cough, day/night-time asthma, and evening PEFR (Fig. 3). Parents' opinion about the effectiveness of treatment were in favour of the active treatment in 13 cases and in favour of placebo in five ($P < 0.05$). Clinicians' opinion about the effectiveness of treatment were in favour of the active treatment in eight cases and in favour of placebo in five (n.s.).

Tolerance

Both treatments were well tolerated. Mild and transient unusual symptoms were reported by four patients in the nedocromil sodium group, e.g. headache and pain, itching, sore throat, and by four patients in the placebo

group, e.g. abdominal pain, headache, and aching and sore throat. No patient complained of the foul taste of either treatment. No significant change in haematological or biochemical parameters after the treatment period was found in both groups.

Discussion

This double-blind placebo-controlled study was performed on children suffering from seasonal pollen asthma, who had asthmatic symptoms for at least 2 weeks before the enrolment, which took place when the pollen count was high. Although the number of patients who completed the trial was only 16 in the nedocromil group and 13 in the placebo group, there are clear statistically significant improvements in the number of parameters evaluated. Indeed, the results show that nedocromil sodium at the dosage of 4 mg four times/day has induced a statistically significant improvement as regards morning tightness ($P < 0.01$), mean morning PEFR values ($P < 0.05$) in comparison with the placebo group. However, the improvement recorded for cough, day/night-time asthma, and mean evening PEFR values on diary cards was not statistically significant.

The relatively short period of 4 weeks' treatment may have attenuated the effectiveness of the drug, which is a mast-cell stabilizer with some anti-inflammatory properties; it should therefore be used for longer periods to achieve more favourable results. We may speculate that if nedocromil is employed not only during, but also before the pollen season when the patients are symptom-free, asthma would be prevented in a more significant way. Our study group already had symptoms when the study was started, the presence of symptoms being among the inclusion criteria for enrolment in the study.

Asthmatics with seasonal symptoms due to pollen allergy tend to be those who have late asthmatic responses when given an inhalation test with pollen out of season, and who have increases in methacholine responsiveness during the pollen season [22]. Nedocromil sodium has been shown to reverse bronchial hyperreactivity in adults during the pollen season [16], to be clinically effective in seasonal allergic rhinitis [23,24], and to significantly inhibit the mast-cell accumulation in the nasal mucosa of grass-allergic patients during the pollen season [25]. In addition, nedocromil sodium inhibits the antigen-induced release of histamine, leukotriene C₄, and prostaglandin D₂ from bronchoalveolar lavage cells of macaques sensitized to *Ascaris suum*, and is at least 200 times more potent than SCG in this animal model [26]. In a double-blind, cross-over study it has recently been demonstrated that the inhalation of nedocromil sodium significantly

prevents the neurotransmitter NKA-induced bronchoconstriction in subjects with asthma [27].

Asthma exacerbation seems to imply airway inflammation that requires adequate additional treatment with drugs with anti-inflammatory properties. In the last decade, inhaled topical steroids achieved an important role in the asthma management. However, oropharyngeal candidiasis, hoarseness, sore throat, and suppression of adrenal function limit their use to severe cases. SCG has been proven effective in exercise-induced asthma, and to have a prophylactic effect if taken during periods of remission in asthmatic children. Nedocromil sodium, due to its anti-inflammatory *in-vitro* properties, is indicated more in cases of asthma exacerbation. The data presented here seems indirectly to support the inflammatory properties of nedocromil sodium.

Although the treatment lasted only 4 weeks, nedocromil was well tolerated, and the untoward effects were similar for both treatments. The unpleasant taste which has been reported in adults was not complained of by our patients. It is of note that children are very sensitive to foul taste, especially of drugs. However, this previously reported side-effect was very recently noted only in 4/188 adults [15].

In conclusion, the data in the present study confirms that nedocromil sodium is an effective drug for the treatment of childhood asthma. We stress that nedocromil sodium was effective in asthmatic children presenting symptoms for at least 2 weeks before the start of the study. Therefore, it should be considered as a first-line drug for the management of childhood asthma.

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