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Does nedocromil sodium have a steroid sparing effect in adult asthmatic patients requiring maintenance oral corticosteroids?

J G GOLDIN, E D BATEMAN

From the Respiratory Clinic, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

ABSTRACT A randomised, double blind, placebo controlled trial of nedocromil sodium was undertaken to assess its corticosteroid sparing effect in 50 adults with asthma who had required an oral corticosteroid dose of (or equivalent to) at least 5 mg prednisolone a day continuously during the preceding year, in addition to inhaled beclomethasone dipropionate and bronchodilators. Patients having corticosteroids other than prednisolone were changed to prednisolone. A four week baseline period was followed by 20 weeks of inhaled nedocromil sodium (16 mg daily) or placebo. After four weeks of the treatment phase an attempt was made to reduce the oral prednisolone maintenance dose by 2·5 mg a fortnight until a dose of 5 mg daily was reached and thereafter by 1 mg a fortnight, provided that there was no significant clinical deterioration as judged by clinic assessments and daily diary cards. Of 50 patients recruited, 47 entered the treatment phase (age range 16–64 years), 24 receiving nedocromil sodium and 23 placebo. The total steroid reduction achieved was 2·5 mg in the nedocromil group and 3 mg in the placebo group, which did not differ significantly. There was no significant change in symptoms, lung function or inhaler use in either group during the study. The number of patients requiring short term upward adjustment of booster doses of oral prednisolone for exacerbations of asthma was similar in the two groups (26 with placebo, 28 with nedocromil). Thus nedocromil sodium does not appear to provide an oral corticosteroid sparing effect in chronic steroid dependent asthma.

Introduction

Nedocromil sodium is a pyranoquinoline dicarboxylic acid derivative that possesses non-bronchodilator anti-asthma properties,[1–10] some of which were reported in the proceedings of a congress on airway inflammation.[1] Pretreatment with nedocromil sodium has been shown to inhibit the bronchoconstrictor effects of exercise,[1–3] sulphur dioxide,[4] cold air,[5,6] and the immediate and late response to allergen provocation.[1–7] It has also been shown to attenuate the increase in histamine airway responsiveness during the grass pollen season in pollen sensitive subjects.[8] A clinical trial in non-steroid dependent asthmatic patients showed improved control of asthma.[9] We have studied the steroid sparing effects of nedocromil in patients requiring oral corticosteroids in addition to beclomethasone dipropionate. The study had a randomised, double blind, placebo controlled design with an active treatment phase of 20 weeks; the patients had severe asthma requiring oral corticosteroids in a minimum dose of 5 mg prednisolone or its equivalent daily over the last year.

Address for reprint requests: Professor E D Bateman, Respiratory Clinic, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa.

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Methods

PATIENTS

Fifty patients with asthma were recruited from the respiratory outpatient clinic at Groote Schuur Hospital (table 1). All patients were aged at least 14 years and had been taking oral prednisolone or an equivalent corticosteroid at a regular daily or alternate day dose averaging at least 5 mg/day for at least one year in addition to regular aerosol and oral

Table 1 *Patients' characteristics on admission to the trial (values are means with ranges in parentheses unless indicated otherwise)*

	Nedocromil sodium (n = 24)	*Placebo (n = 23)*
Age (y)	41·5 (20–64)	39·4 (16–60)
Sex (female : male)	18 : 6	17 : 6
Duration of asthma (y)		
Childhood onset ⩽13 years	27·4 (15–52)	18·8 (7–40)
n	8	11
Adult onset > 13 years	16·6 (1·3–40)	11·4 (4–25)
n	16**	12**
Severity* of symptoms during last 12 months (n)		
Mild	13	3
Moderate	10	15
Severe	1	4
Very severe	0	1
Peak flow (l/min)		
Before bronchodilator	372 (140–620)	319 (200–480)
After bronchodilator	396 (170–640)	355 (215–500)
FEV1 (l)		
Before bronchodilator	1·79 (0·45–4·69)	1·54 (0·5–2·85)
After bronchodilator	1·9 (0·55–3·0)	1·79 (0·56–3·01)
Reversibility in FEV_1 (%)	15·9 (−22 to 52)	18·2 (−3 to 86)
Daily dose of oral prednisolone or prednisone (mg)	8·23 (5–20)	8·59 (3·75–20)
Medication before admission (n)		
Oral steroid	24	23
Inhaled steroid	17	15
Oral theophylline	24	22
Salbutamol spandettes	9	17
Inhaled bronchodilator	24	23
Nasal steroid	0	1
Nasal sodium cromoglycate	0	1

*See under "Methods" for scoring system.
With the exception of duration of asthma ($p < 0·05$ for values marked ** versus childhood onset nedocromil sodium and placebo groups) no statistically significant differences exist between the nedocromil sodium and placebo groups for the features shown above.

bronchodilator treatment. None was taking inhaled sodium cromoglycate or ketotifen. All had been stable (free of acute severe exacerbations requiring increased steroid dosage), and had been free of respiratory infections for at least six weeks before their entry into the trial. Patients also had to fulfil the following criteria: either (*a*) clinical evidence of an asthma attack on at least one occasion in the last six months or (*b*) a forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), or peak expiratory flow (PEF) less than 80% of the predicted value, and a 15% improvement in FEV_1 after inhalation of two actuations of a $beta_2$ adrenergic bronchodilator aerosol during the previous six months.

A severity of asthma score was used to indicate symptoms and functional state (interference with daily activities) during the last 12 months. The score did not take account of the number and doses of asthma medications used (all patients were taking similar combinations of these—table 1) or the results of lung function tests. Sixteen patients were scored as having mild asthma (occasional asthma symptoms and no impairment of usual activities), 25 as having moderate asthma (limitation of some activities with easily controlled symptoms daily), five as having severe asthma (daily symptoms that interfered with usual activities) and one as having very severe asthma.

STUDY DESIGN

Patients were instructed to inhale regular doses of $beta_2$ adrenergic stimulants, with additional doses as considered necessary to control their asthma. The doses of inhaled steroid (beclomethasone dipropionate) and oral bronchodilators were kept constant throughout the study. Those having alternative forms of corticosteroids changed to an equivalent dose of prednisolone. Antibiotics could be used to treat intercurrent infection. Patients completed daily diary cards with details of asthma severity score, use of the test and other medications, and the results of peak expiratory flow readings. The following symptoms were recorded and scored on a five point scale: (*a*) daytime symptoms (0 indicating no symptoms, 1 occasional wheeze or breathlessness quickly relieved by bronchodilator aerosol, and 4 severe symptoms resulting in inability to work or engage in usual activities); (*b*) morning tightness (1 indicating slight tightness and 4 earlier awakening than normal owing to wheeze or cough, necessitating use of bronchodilator aerosol more than once between waking and measurement of morning PEF); (*c*) nocturnal symptoms (1 indicating awakening on one occasion in the night because of wheezing or cough for less than one hour not necessitating use of a bronchodilator aerosol and 4 being awake most of the night because of wheezing and cough). The best of

three PEF measurements were recorded three times daily.

At the end of a four week run in period patients were allocated on the basis of a randomised coding sheet to receive double blind either nedocromil sodium (2 mg per actuation) or placebo delivered by metered dose aerosol at a dose of two actuations four times daily.

After four weeks of treatment, repeated attempts were made to reduce the patients' maintenance dose of oral prednisolone. In those having more than 5 mg the daily dose was reduced by 2·5 mg at each fortnightly visit. Those having 5 mg or less reduced their daily dose by 1 mg at each visit.

Patients attended at two weekly intervals on 10 occasions (total treatment period 20 weeks), and at each visit the severity of asthma, presence of unusual symptoms, and pulmonary function were recorded.

Lung function tests were performed by experienced technicians using the same spirometer (Vitalograph) for FEV_1 and FVC and peak flow meter (Wright's) for PEF. Inhaled bronchodilator treatment was withheld for four hours before the lung function tests. When this was not possible the lung function record for that visit was excluded from the analysis.

ACUTE ASTHMA ATTACKS

Patients whose asthma deteriorated during the double blind period, to the extent that parenteral corticosteroid or theophylline was needed or admission to hospital was required, were considered to be treatment failures and were withdrawn. When, however, the attack was associated with pyrexia and cough productive of purulent sputum it was considered to be infective rather than a treatment failure; when symptoms subsided the steroid was reduced over two weeks to the dose preceding the infection and further systematic weaning was then attempted according to the study protocol. In most instances the decision to give parenteral treatment was made by doctors in the emergency service of the hospital rather than by the investigators but it was always given when PEF fell and remained below 50% of predicted values, and when nebulisation of fenoterol (1 mg in 4 ml normal saline) failed to achieve a sustained response.

ANALYSIS

Overall assessments, asthma severity scores recorded at the clinic, and asthma symptoms recorded on the diary cards were analysed with the Mann-Whitney U test. Results of pulmonary function tests and use of oral corticosteroids and inhalant bronchodilators were analysed with Student's *t* test. The consistency of the findings was checked by parametric and non-parametric methods, and two tailed tests using a 95% level of significance were used throughout.

The primary variables used to assess efficacy were reduction of oral corticosteroids, diary card symptom scores, PEF, and concomitant use of inhaled bronchodilators. Global assessments combining all these factors were made by the patient and clinician at the end of the trial. Data from each visit were analysed and in the case of diary cards the mean for each two week period of treatment was used. Data were entered on to computer files and checked manually against the original record forms. Patient withdrawals were handled according to the reason for withdrawal. If it was due to asthma, the patient was included at the highest value for asthma severity at the clinic and global assessment. For diary card recordings, the mean of the last three days prior to withdrawal was taken as the final or end point value of the study. All available data for patients withdrawn for other reasons and from patients with missing data were included in the analysis.

Results

DETAILS OF THE PATIENTS

Three of the 50 patients selected for entry into the trial did not enter the treatment period (two because of non-cooperation and one because of abnormal biochemistry results) and these patients were excluded from the analysis. Of the 47 patients (35 females and 12 males) who entered the treatment period, 24 were randomly allocated to receive nedocromil sodium and 23 placebo. The patients' characteristics on admission were similar for the two treatment groups (table 1). There was no difference in mean values of FEV_1, FVC, or PEF and no difference in mean oral steroid dosage (table 1) or beta agonist consumption between the nedocromil sodium and the placebo group. Nine patients were withdrawn during the treatment phase of the study for the following reasons: Sudden deterioration (two in each group), gradual deterioration (one in the nedocromil sodium group) and non-cooperation (two in each group). Compliance, as assessed by inspection of residual inhaler contents at each visit and by regular theophylline estimations, was good in the remaining patients.

EFFECTS OF NEDOCROMIL SODIUM

There were no significant differences between the nedocromil sodium and the placebo group for FEV_1, FVC, or PEF measurements at the clinic visits or in diary card PEF measurements, symptom scores, or inhaler use at any time (table 2, figs 1 and 2). The mean changes in symptoms, lung function, and inhaler use during the course of the study were small and inconsistent. Corticosteroid use, as recorded at clinic visits and on diary cards, declined progressively in both treatment groups (fig 3). The mean steroid reduction in the nedocromil and placebo groups (2·5

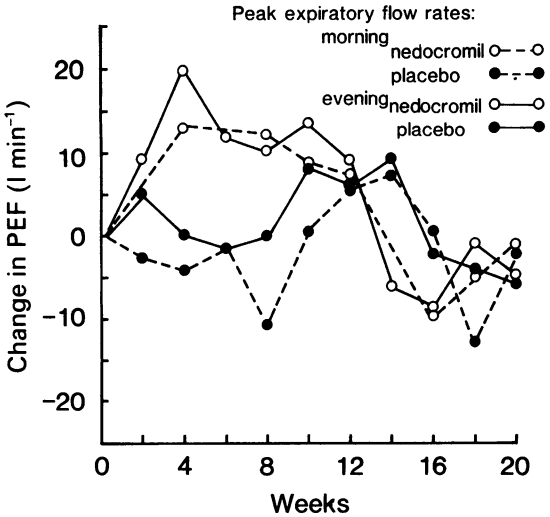

Fig 1 *Mean peak expiratory flow rates (PEF) recorded on diary cards during the double blind treatment phase expressed as an increase (positive values) or decrease (negative values) compared with values during the baseline period (n = 24 on entry).*

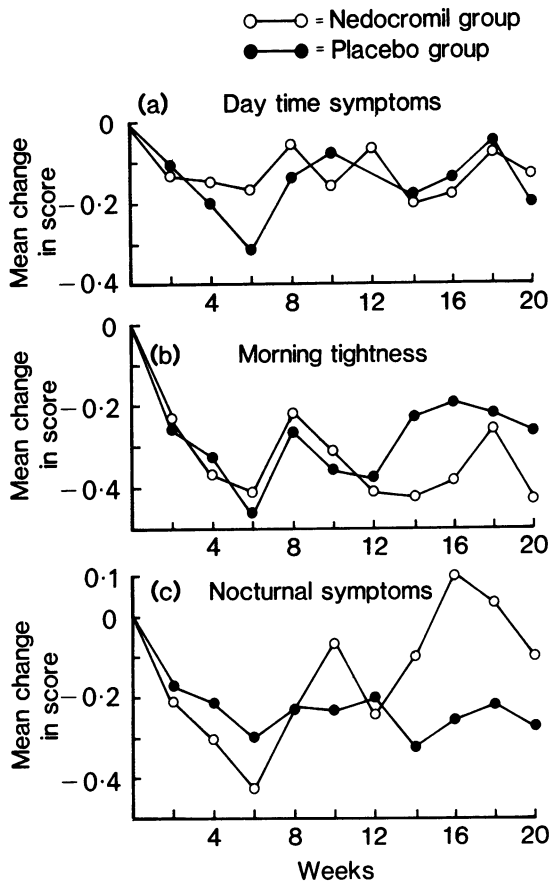

Fig 2 *Mean change in mean symptom score for nedocromil sodium and placebo groups during the treatment phase expressed as deterioration (negative values) and improvement (positive values) compared with the baseline period (initial n = 24 for nedocromil sodium and 23 for placebo group).*

and 3 mg) did not differ significantly (p = 0·12 and 0·13). The oral steroid doses at the start and the end of the trial did not differ significantly between the two groups (p = 0·6 and 0·5). Mean values were lower than the median values as some patients in each group required short term upward adjustment or booster doses of up to 30 mg of oral predisolone daily for exacerbations of asthma, in some as they attempted to reduce their maintenance dose and in some in association with infection (fig 3). The increases in steroid dose occurred on 26 occasions in the placebo group and on 28 in the nedocromil sodium group (difference NS). There was also no effect of nedocromil sodium when the data were analysed according to age of onset of asthma (childhood onset versus onset after the age of 13 years).

Adverse effects Twenty five patients reported unusual symptoms: 14 taking nedocromil sodium and five taking placebo reported an abnormal (usually bitter) taste, and five and four respectively an aftertaste. Three taking nedocromil sodium reported a cough. No severe symptoms or blood or urine

Table 2 *Lung function (means with ranges in parentheses) on admission and at the end of the trial (at clinic visit)*

	Group	*PEF (l/min)*		*FVC (l)*		*FEV (l)*	
Admission	Nedocromil sodium (n = 24)	372	140–620	2·86	1·43–5·39	1·79	0·45–4·69
	Placebo (n = 23)	319	200–480	2·63	1·19–3·85	1·54	0·5–2·9
	p*	0·25		0·55		0·34	
End of trial	Nedocromil sodium (n = 19)	329	150–610	2·91	1·1–4·8	1·71	0·70–4·7
	Placebo (n = 19)	294	160–465	2·64	1·0–3·9	1·42	0·44–3·18
	p*	0·43		0·42		0·46	
Admission *v* end of trial (p**)	Nedocromil sodium (n = 19)	0·33		0·67		0·72	
	Placebo (n = 19)	0·27		0·57		0·42	

p* *t* test; **paired *t* test.
PEF—peak expiratory flow; FVC—forced vital capacity.

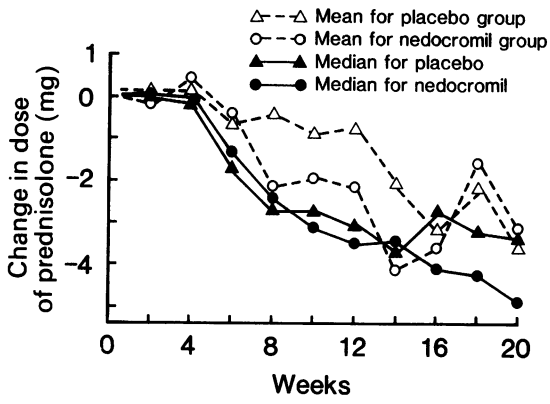

Fig 3 *Reduction in prednisolone dose in nedocromil sodium and placebo groups during the treatment phase expressed as change from doses used during the baseline period (initial n = 24 for nedocromil sodium, 23 for placebo group).*

abnormalities occurred and none of the patients was withdrawn because of suspected adverse reactions.

Discussion

There is little information on the effect of nedocromil sodium in patients on inhaled beclomethasone dipropionate but what is available suggests that its steroid sparing effects are limited.[1] The aim of our study was to answer the important clinical question of whether nedocromil sodium might be used to replace or reduce oral corticosteroid treatment in steroid dependent asthmatic patients. Patients were selected for the persistent rather than intermittent nature of their symptoms (that is, chronic asthma), and all required both standard doses of inhaled beclomethasone dipropionate and daily or alternate day doses of oral prednisolone or an equivalent (mean > 8 mg/day) for more than one year. The need for maintenance corticosteroid treatment in these patients had been established historically over many visits in the clinic, where as a matter of routine regular attempts are made to reduce oral steroid treatment.

This dependence on oral corticosteroids was substantiated during the trial because only modest reductions were possible in the placebo treated patients. Some patients were unable to reduce the steroid dose at all, and some who did had to be withdrawn because of repeated episodes of deteriorating asthma. On the other hand, because all were aware of the adverse effects of oral corticosteroids, they shared the desire to reduce the dose if possible and their compliance with the requirements of the protocol was good throughout. This factor and the design of the trial created a bias in favour of reducing steroids. The trial moreover was of sufficient duration and had a sufficiently circumscribed end point to provide a conclusive result. The analysis of the effects of nedocromil sodium in asthma of childhood onset was made because of the acknowledged importance of allergic mechanisms in childhood asthma.[1] Nedocromil sodium has been shown to have anti-allergic properties that are at least as great as those of sodium cromoglycate.[1] Thus on the basis of this study we conclude that nedocromil sodium does not provide an oral corticosteroid sparing effect in the management of chronic asthma in adults, regardless of whether this developed in childhood or during adult life.

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