

Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma

U.G. Svendsen, H. Jørgensen

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ABSTRACT: Thirty five asthmatic patients were included in a randomized, double-blind, placebo-controlled, parallel group study of inhaled nedocromil sodium (4 × 4 mg daily) as an additional treatment to high dose (≥1,000 µg) inhaled corticosteroids in the management of bronchial asthma. Following a four week baseline, patients received nedocromil sodium (17) or placebo treatment (18) for eight weeks.

Five patients (four in the group subsequently randomized to nedocromil sodium) used short course oral corticosteroid therapy during the baseline and four placebo treated patients used oral steroid therapy during treatment. Fifteen patients (11 nedocromil sodium) reported unusual symptoms. Two nedocromil sodium treated patients were withdrawn owing to treatment taste and vomiting. Statistically significant treatment differences in favour of nedocromil sodium were seen for daytime symptoms ($p=0.03$) and morning peak expiratory flow (PEF) ($p=0.012$) during weeks 5-8, and for clinician opinion ($p=0.02$). Patient opinion ($p=0.053$) and evening PEF ($p=0.08$) failed to reach statistical significance. Eight out of fifteen and three out of seventeen patients considered nedocromil sodium and placebo, respectively, to be very or moderately effective.

The results indicate that the addition of nedocromil sodium (4 mg four times daily) to moderate to severe asthmatics not fully controlled on a regimen of ≥1,000 µg inhaled corticosteroids and inhaled bronchodilators can produce improvements in symptoms and pulmonary function.

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Nedocromil sodium is the disodium salt of a pyranoquinoline dicarboxylic acid developed for topical use in the treatment of asthma [1]. It has been shown to be effective in inhibiting the immediate [2-4] and late reactions [3, 4] in response to antigen challenge, and bronchoconstriction induced by exercise [5-7] and SO₂ [8, 9] challenge. Nedocromil sodium also reduces bronchial reactivity in pollen sensitive individuals during the pollen season [10, 11]. In clinical trials therapeutic efficacy has been demonstrated over periods from four weeks to twelve months [12].

Many patients with severe asthma require high dose inhaled corticosteroids to control their condition; however, some clinicians regard the use of high doses of inhaled steroids as potentially hazardous [13-15]. A recent review [16] of the adverse effects of inhaled corticosteroids indicates that oral candidiasis (frequency 5-13% in adults) and dysphonia are dose dependent, and that adrenal suppression may occur when the daily dose exceeds 1,500 µg. An additional medication of a non-steroidal nature

which would reduce the amount of inhaled corticosteroids needed to control the patient's condition might be a very useful adjunct therapy.

The aim of the present study was, thus, to compare the effects of additional treatment with either nedocromil sodium or placebo in patients with moderate to severe asthma, who had room for improvement in their pulmonary function despite taking at least 1,000 µg inhaled beclomethasone dipropionate daily.

Patients

Asthmatic patients [17] of either sex and at least 18 yrs of age were selected for an eight week, double-blind, parallel group comparative study. Patients were included if on entry, or in the previous 12 months, they had demonstrated at least 15% reversibility to the pre-bronchodilator value of forced expiratory volume in one second (FEV₁) following a standard dose of inhaled

bronchodilator, had used 1,000–2,000 µg inhaled corticosteroid daily at a steady dose for at least one month before the trial and required an inhaled bronchodilator. Only patients who had room for improvement in their pulmonary condition were included. This improvement was manifest by a baseline FEV₁ of less than 70% predicted normal [18], a 15% variability in peak expiratory flow rate (PEF) either from day to day or morning to evening, or a total baseline diary card symptom score of at least 30. Patients who had had a respiratory infection within the previous six weeks, a recent marked seasonal asthma exacerbation, or used sodium cromoglycate or oral corticosteroids in the four weeks before the study baseline were excluded from the study. The patients were to be proficient in the use of a pressurized aerosol, co-operative and able to keep a daily diary card.

Methods

An admission form was completed on entry providing details of age, sex, height, weight, duration and type of bronchial asthma, previous medical history, details of any abnormal finding on physical examination, severity of asthma (four point scale ranging from mild to very severe), pulmonary function tests (PEF, forced vital capacity (FVC) and FEV₁) and reversibility in FEV₁. Histamine bronchial provocation (PC₂₀-histamine) was measured as described previously [19].

Patients returned to the clinic at the end of a four week baseline and were randomly allocated to one of two treatment groups for an eight week treatment period. Patients received 2 mg nedocromil sodium or a matching placebo (propellants and excipients only) delivered *via* a metered dose inhaler. The dosage was two actuations of the inhaler four times daily.

At the end of baseline clinic visit and after four and eight weeks of treatment asthma severity, pulmonary function and PC₂₀ to histamine were assessed. Details of any unusual symptoms and of the use of any rescue therapy were obtained. At the final visit, the patient and the clinician gave their opinion on how effective they considered the test treatment to have been (five point scale ranging from "very effective" to "made condition worse").

During the baseline and test treatment period the patients continued with their usual therapy and kept a daily diary card recording night-time asthma, morning tightness, daytime asthma and cough using five point severity scales, the highest of three measurements of morning (on waking) and evening (before going to bed) PEF using mini Wright peak flow meters obtained from Airmed (Harlow, UK) and use of all medications, including inhaled bronchodilators and oral and inhaled corticosteroids. Test treatment use was also recorded during the treatment phase. Patients using oral bronchodilator therapy were requested to keep to the same daily dose throughout the trial. The use of oral steroid rescue therapy, provided the course lasted seven days or less, was permitted and assessed as an efficacy variable.

All patients had the purpose of the trial explained and their written consent was obtained. Written approval was obtained from the hospital Ethical Committee and the study was conducted in accordance with the principles established by the Declaration of Helsinki.

Statistical methods

Pulmonary function and PC₂₀ measurements (after log transformation) were analysed using Student's t-test, all other variables were analysed using the Mann-Whitney U-test. Two-tailed tests were used throughout at the 95% level of significance.

The data were analysed using changes from baseline (end of baseline visit for clinic data and the mean of the baseline for diary card data). Diary card analyses were based on the mean of the data from each four weeks of treatment (weeks 1–4 and 5–8). All comparisons were between treatment groups. The primary variables were the patient's daily assessment of their condition (symptom scores, PEF and use of concomitant medication), patient and clinician opinion of treatment effectiveness and PC₂₀. The primary period was the last four weeks of treatment.

Patient withdrawals due to lack of efficacy were included provided test treatment had been used for at least seven days. Maximum scores for clinic assessments (scores of 4 for asthma severity and 5 for opinion of efficacy) and the mean scores for the three days before withdrawal for diary card variables have been used in subsequent analyses.

Results

Forty two patients were recruited into the study. Six failed to satisfy the entry criteria and one moved outside the trial area. Thus, 35 patients entered the treatment period, of whom 17 were allocated to nedocromil sodium and 18 to placebo treatment. Asthma was moderate or moderately severe in 16 nedocromil sodium and 12 placebo treated patients. All, with the exception of five nedocromil sodium treated patients, were intrinsic asthmatics (table 1). Reversibility in FEV₁ at admission was 26% in the nedocromil sodium group and 18% in the placebo group. Mean daily dosage of inhaled steroids in the nedocromil sodium group was 1,247 µg compared with 1,067 µg in the placebo group. Thirteen of the patients randomized to nedocromil sodium used beclomethasone dipropionate (15 in the placebo group) and three used budesonide (3 in the placebo group). One nedocromil sodium treated patient used both beclomethasone dipropionate and budesonide. All patients, except one, used inhaled bronchodilators and five nedocromil sodium and two placebo treated patients used theophylline tablets. There were no significant differences ($p > 0.05$) in baseline diary card or clinic visit variables between the two treatment groups (fig. 1–3).

Table 1. - Patient characteristics at admission

		Nedocromil sodium	Placebo
Sex	male	7	9
	female	10	9
Age yrs	mean	52	62
	range	22-65	23-75
Asthma type	intrinsic	12	18
	mixed*	4	0
	not recorded	1	0
Asthma severity	moderate	14	7
	moderate/severe	2	5
	severe	1	5
	not recorded	0	1
Duration yrs	mean	12.0	9.4
	range	1-30	1-43
Inhaled corticosteroid Daily dose	1000 µg	13	16
	1200 µg	1	1
	1500 µg	1	0
	2000 µg	2	1
FEV ₁ l Pre-bronchodilator	mean**	1.47	1.14
	range	0.68-3.62	0.58-2.58
% reversibility	mean	26	18
	range	-6-63	-1-49

*: allergic and non-allergic causative factors present; **: n=17 for FEV₁ determinations in the placebo group; FEV₁: forced expiratory volume in one second.

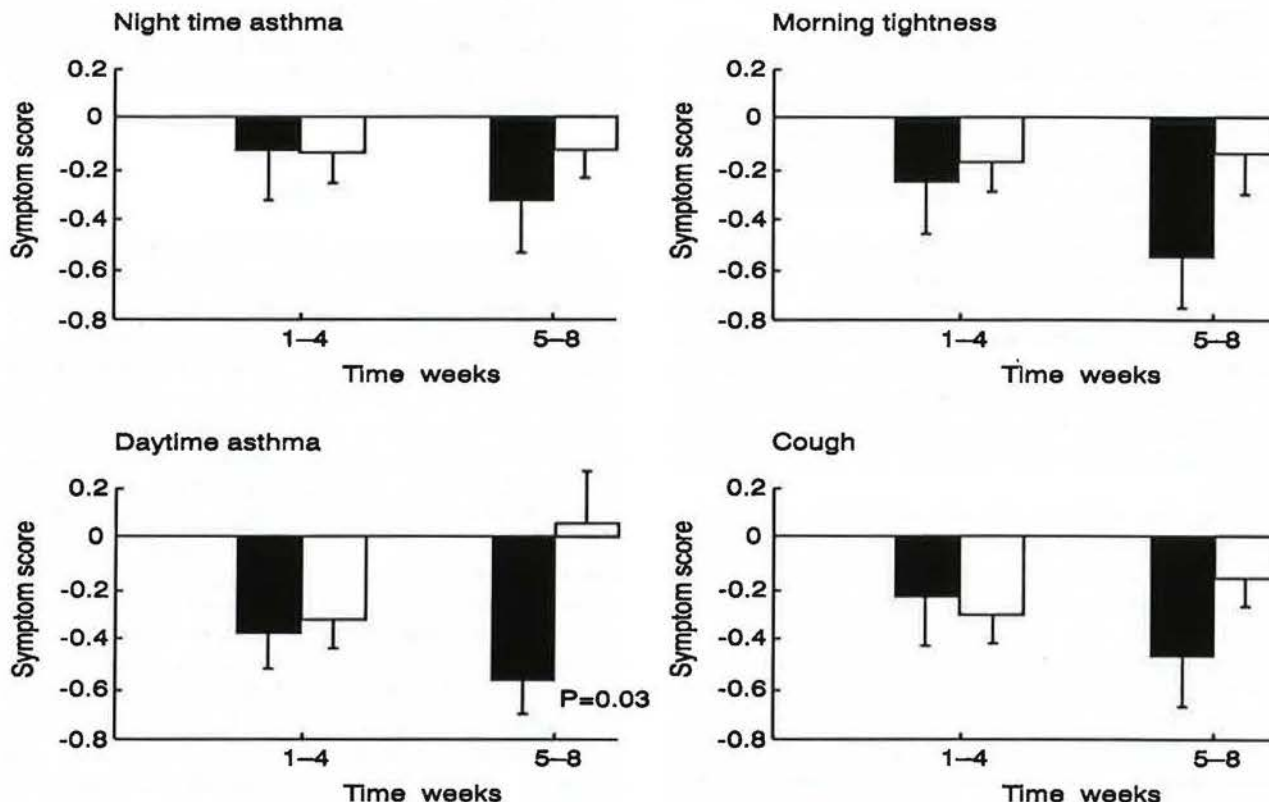


Fig 1. - Mean change (\pm SEM) from baseline in asthma symptom severity scores (night-time asthma, morning tightness, daytime asthma and cough) calculated from the daily diary cards. A significant difference ($p=0.03$) in favour of nedocromil sodium was seen for daytime asthma during weeks 5-8 (Mann-Whitney U-test). Scale: 0 = none to 4 = severe. ■: nedocromil sodium; □: placebo. Baseline values: night-time asthma - nedocromil sodium 1.20 ± 0.23 , placebo 0.98 ± 0.20 ; morning tightness - nedocromil sodium 1.84 ± 0.16 , placebo 1.34 ± 0.15 ; daytime asthma - nedocromil sodium 1.38 ± 0.18 , placebo 1.20 ± 0.19 ; cough - nedocromil sodium 1.11 ± 0.25 , placebo 1.06 ± 0.19 .

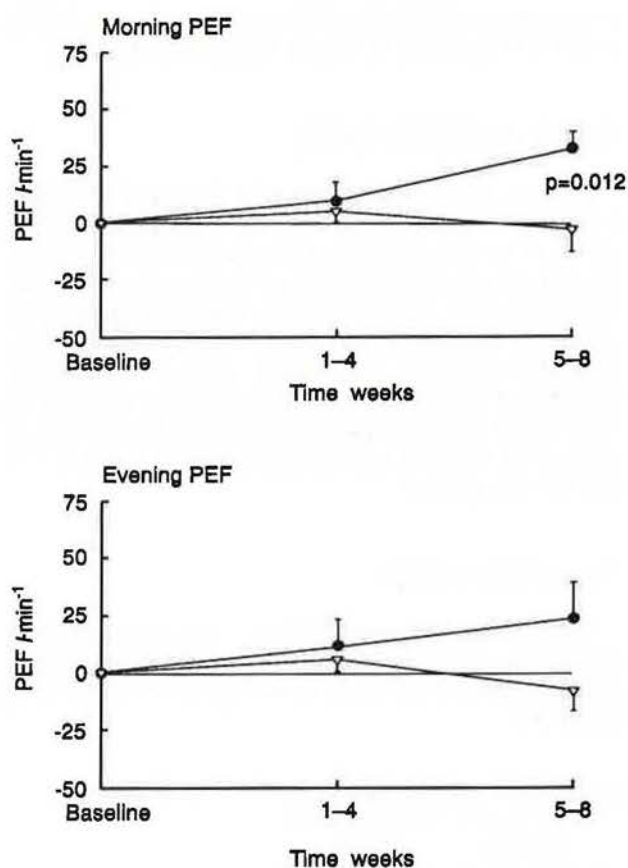


Fig. 2. - Mean change (\pm SEM) from baseline in peak expiratory flow rate (PEF) calculated from the daily diary cards. A significant difference ($p=0.012$) in favour of nedocromil sodium was seen for morning peak expiratory flow rate during weeks 5-8 (Student's *t*-test). ●: nedocromil sodium; ▽: placebo. Baseline values: morning PEF - nedocromil sodium 256.1 ± 26.9 , placebo 232.9 ± 22.1 ; evening PEF - nedocromil sodium 292.7 ± 24.9 , placebo 254.1 ± 23.9 .

Eleven nedocromil sodium treated patients reported the unusual symptom of bitter/bad taste. Three of these patients reported dizziness (1) and vomiting (2). Four placebo treated patients also reported a bitter taste with treatment. Five patients in total were withdrawn, three from the nedocromil sodium group (owing to bitter taste, bad taste and vomiting, and gradual deterioration of asthma) and two from the placebo group (non-cooperation and treatment failure).

The majority of the patients took the test treatment as specified. One nedocromil sodium treated patient received four instead of eight inhalations per day. Test treatment usage (inhalations per day \pm SD) during weeks 1-4 and 5-8 was 7.28 ± 1.14 and 7.29 ± 1.44 , respectively, for the nedocromil sodium group (placebo group: 7.89 ± 0.20 and 7.74 ± 0.78). Four patients in the nedocromil sodium group (one of whom was subsequently withdrawn owing to gradual deterioration in asthma) and one patient in the placebo group used oral steroid during the baseline period. Four placebo treated patients required courses of oral steroid during weeks 5-8 of the test treatment period.

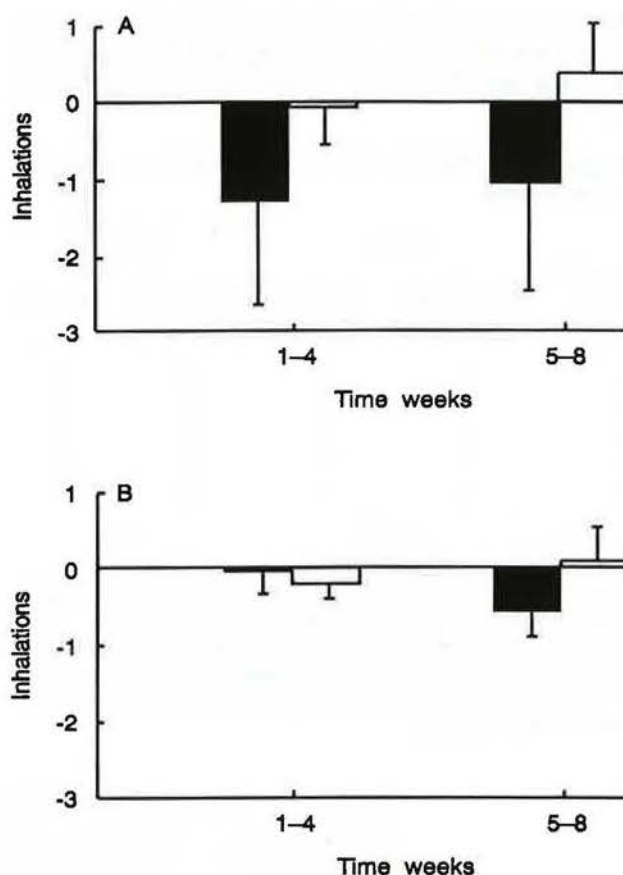


Fig. 3. - Mean change (\pm SEM) from baseline in (A) daytime and (B) night-time inhaled bronchodilator use (number of inhalations) calculated from the daily diary cards. There were no significant ($p>0.05$) differences. ■: nedocromil sodium; □: placebo. Baseline values: A) nedocromil sodium 8.21 ± 1.48 , placebo 7.95 ± 1.06 ; B) nedocromil sodium 2.25 ± 0.45 , placebo 2.02 ± 0.59 .

Asthma symptom scores

The changes from baseline in diary card asthma symptom scores were similar for the two treatment groups during weeks 1-4 ($p>0.05$). During weeks 5-8, the mean reduction in scores from baseline was greater for the nedocromil sodium group compared to the placebo group - the severity of night-time symptoms fell by 28%, morning tightness by 30%, daytime asthma by 41% and cough by 44% (two and three times the improvement recorded with placebo treatment) - reaching statistical significance for daytime asthma ($p=0.03$).

Morning and evening PEF

Morning and evening PEF increased to a small extent in both treatment groups during weeks 1-4. During weeks 5-8 there was an increase from baseline in morning and evening PEF in the nedocromil sodium group of 33 l·min⁻¹ and 24 l·min⁻¹, respectively. PEF decreased from baseline during this time in the placebo group. The

between treatment difference was significantly in favour of nedocromil sodium for morning peak flow ($p=0.012$). Evening peak flow failed to reach statistical significance ($p=0.08$).

Table 2. — Patient and clinician opinion of treatment effectiveness

Opinion score	Patient		Clinician	
	Nedocromil sodium	Placebo	Nedocromil sodium	Placebo
1	3	2	2	1
2	5	1	4	1
3	3	4	4	1
4	4	9	5	13
5	0	1	0	1
p-value	0.053		0.02	

Score: 1 = very effective; 2 = moderately effective; 3 = slightly effective; 4 = no effect; 5 = made condition worse. Three patients not included owing to withdrawal: non-co-operation (placebo), unusual symptom and treatment taken for less than 7 days (nedocromil sodium) and gradual deterioration of asthma (nedocromil sodium).

treatment group differences at baseline ($p=0.41$), during weeks 1–4 ($p=0.68$) or during weeks 5–8 ($p=0.28$).

Opinion of treatment efficacy

Patient and clinician opinion strongly favoured nedocromil sodium (table 2). Fifty three percent (8 out of 15) of nedocromil sodium compared with 18% (3 out of 17) of placebo treated patients considered the treatment very or moderately effective ($p=0.053$). Clinician opinion of treatment efficacy significantly ($p=0.02$) favoured nedocromil sodium - assessing nedocromil sodium as very or moderately effective in 40% (6 out of 15) of patients compared with a very or moderately effective assessment in 12% (2 out of 17) of the placebo patients.

PC_{20} -histamine values

During the treatment period, the changes from baseline were not significantly different between the two groups ($p=0.39$ at week 4 and $p=0.76$ at week 8) (table 3).

Table 3. — $\log_e PC_{20}$ (\pm SEM) values from histamine provocation tests

Treatment period	Nedocromil sodium	Placebo	p-value
Baseline	-1.49 \pm 0.32	-1.75 \pm 0.26	0.49
Increase from baseline			
Weeks 1–4	0.13 \pm 0.19	0.35 \pm 0.17	0.39
Weeks 5–8	0.17 \pm 0.20	0.26 \pm 0.21	0.76

PC_{20} : provocative concentration of histamine producing a 20% fall in forced expiratory volume in one second.

Inhaled bronchodilator use

Daytime use decreased in both treatment groups during weeks 1–4, but more so in the nedocromil sodium group (fig. 3). Night-time use decreased by 0.25 inhalations in the placebo group but remained unchanged in the nedocromil sodium group. The reduction in daytime use (>1 inhalation) was sustained in the nedocromil sodium group during weeks 5–8 and night-time use was also reduced. During this time, use of inhaled bronchodilator increased in the placebo treated group. Total day- and night-time use decreased by 1.72 inhalations in the nedocromil sodium group compared with an increase of 0.41 inhalations in the placebo group. None of the between treatment differences were statistically significant, however.

Inhaled steroid use

The patients used their inhaled corticosteroids as prescribed and at a constant dose, with no significant

Pulmonary function

Both treatment groups showed an improvement during the treatment period in PEF of approximately 30 $l \cdot \text{min}^{-1}$ but little change in FEV_1 and FVC. No significant differences between the treatment groups were seen.

Discussion

The present study compared inhaled nedocromil sodium or placebo as additional treatment to high-dose inhaled corticosteroids in the management of asthma. Overall the results favoured nedocromil sodium - during the final four weeks of treatment night-time asthma severity was reduced by 28%, morning tightness by 30%, daytime asthma by 41% and cough by 44% (two and three times the improvement recorded with placebo treatment). Daily morning and evening peak flow improved by approximately 30 $l \cdot \text{min}^{-1}$. Clinician opinion significantly favoured nedocromil sodium, and the

reduction in daytime symptoms and increase in morning PEF were statistically significant. These improvements were concurrent with a reduction in inhaled bronchodilator use. No effect of treatment was seen on responsiveness to histamine. Eight weeks is, however, a relatively short time to detect changes in bronchial responsiveness and longer observation periods might have shown differences as a result of treatment.

The patients received the study treatments after randomization which, based on patient characteristics and baseline assessment, resulted in two well-matched groups. The patients had low values for FEV₁. The majority were in the 55+ yrs age group and over half had suffered asthma for at least five years. Historical data confirming the lack of a fixed obstruction was available for those patients who did not record $\geq 15\%$ reversibility in FEV₁ on entry. The patients also demonstrated reversibility in PEF (23% and 22% for the nedocromil sodium and placebo treatment groups, respectively). Three nedocromil sodium (the fourth was excluded from the efficacy analyses) and one placebo treated patient received short reducing courses of oral steroids during the baseline. It was not thought that baseline treatment influenced subsequent assessments since disease severity (as assessed from diary card data), current treatment and patient history were similar in both groups.

We considered the possibility that several patient-related factors may have influenced the treatment phase. Treatment compliance, however, was excellent and use of inhaled corticosteroids did not alter significantly during the study. Taste did not appear to affect treatment compliance adversely or - given the parallel group comparative design - compromise the blinding of the study. A review of the diary card and patient and clinician opinion data indicated that the four or five nedocromil sodium treated patients who may have had an allergic component to their asthma did not influence the results in favour of their treatment and, if anything, performed less well than the majority. Finally, the four patients who received short courses of oral steroids during weeks 5-8 (the primary period of assessment of efficacy) were all taking placebo treatment - hence any improvement would have reduced the apparent comparative efficacy of nedocromil sodium, and not increased it.

Nedocromil sodium has been added to maintenance bronchial asthma therapy in patients receiving low to moderate dose inhaled steroids [20-22]. In these studies the results favoured nedocromil sodium treatment with significant changes in diurnal variation in PEF [20], in PEF, FEV₁, FVC and patient opinion [21] and, in a large multicentre study, in virtually all measures of efficacy [22]. At variance with an earlier 4 mg twice daily cross-over study [23], no deterioration of symptoms occurred when beclomethasone dipropionate treated patients (400 μg) were transferred to 4 mg nedocromil sodium four times daily [24], suggesting that in these patients - all of whom were similar in age [20-24], severity [21, 22] and FEV₁ [23, 24] on admission - the four times daily regimen is to be preferred.

Previous research [25] in intrinsic asthmatics has shown a comparable effect of nedocromil sodium

and inhaled steroids on responsiveness to methacholine and symptoms but not on the effect of a deep inspiration on airflow obstruction. This suggests that, although both drugs possess anti-inflammatory activity, their effect on bronchial responsiveness may be by different mechanisms and that their concomitant use may result in additive effects [25] - as shown in the present study. Recent preliminary data in hyperresponsive allergic rhinitis [26] supports this hypothesis. The other studies which have shown nedocromil sodium to provide either the therapeutic equivalent of low dose inhaled corticosteroid [24, 27, 28] or additional benefit from their concomitant use [21, 22, 29] have not explored, beyond additional anti-inflammatory activity, the potential mechanism of action. The mechanism by which nedocromil sodium improved symptoms and lung function in the present study is open to conjecture. Pharmacological studies [30, 31] indicate that whilst inhibition of cell activation, chemotaxis and oedema may be common to both drugs, one clearly is not adding "more of the same". It is possible that nedocromil sodium may exert its influence *via* local axon and vagal reflex mechanisms [32-34].

In the present study the majority of the patients were intrinsic asthmatics, emphasizing that nedocromil sodium is not a drug solely for use in atopic asthmatics [23]. Inhaled therapy with steroids is often required for life, and doses in excess of 1,000 μg daily are now employed regularly. Although the adverse effect profile for inhaled corticosteroids is much better than for the oral medication, there is still concern that systemic effects may present problems after longer periods of treatment [13-15]. Thus, continued studies of non-steroidal alternatives are of high priority.

Conclusion

Inhaled nedocromil sodium (16 mg·day⁻¹) as additional treatment to high dose inhaled corticosteroids (above 1,000 μg ·day⁻¹) produced improvements in symptoms and pulmonary function in moderate to severe asthmatics not fully controlled on their current regimen. The treatment was generally well-tolerated but many patients commented on a bitter taste, particularly with nedocromil sodium.

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- Nedocromil sodique en inhalation, comme traitement complémentaire à des doses élevées de corticostéroïdes par inhalation, dans le traitement de l'asthme bronchique. U.G. Svendsen, H. Jorgensen.*
- RÉSUMÉ: Trente-cinq patients asthmatiques ont été inclus dans une étude randomisée en double aveugle, avec contrôle par placebo, et conduite en parallèle au moyen de nedocromil sodique inhalé (4 x 4 mg par jour), comme traitement complémentaire à de fortes doses (≥ 1.000 µg) de corticostéroïdes par inhalation dans le traitement de l'asthme bronchique. Après une période d'observation basale de quatre

semaines, les patients ont reçu le nedocromil sodique (17) ou le placebo (18) pendant huit semaines.

Cinq patients (quatre dans le groupe ultérieurement randomisé vers le nedocromil sodique) ont utilisé un traitement aux corticostéroïdes oraux pendant une brève durée au cours de la période d'observation initiale. Quatre patients traités au placebo ont eux aussi reçu des stéroïdes par voie orale pendant le traitement. Quinze patients (dont 11 sous nedocromil sodique) ont fait état de symptômes inhabituels. Deux patients traités au nedocromil sodique ont dû être écartés à cause du mauvais goût du traitement et de vomissements. Des différences statistiquement significatives en faveur du nedocromil sodique ont été observées en ce qui concerne les

symptômes diurnes ($p=0.03$) et le DEP du matin ($p=0.012$) pendant les semaines 5 à 8, ainsi que pour l'opinion du clinicien ($p=0.02$). L'opinion du patient ($p=0.053$) et le DEP vespéral ($p=0.08$) n'ont pas atteint une signification statistique. 8/15 et 3/17 patients ont considéré respectivement le nedocromil sodique ou le placebo comme étant très ou moyennement efficace.

Ces résultats indiquent que l'addition de nedocromil sodique (4 mg quatre fois par jour) à des sujets asthmatiques modérés à sévères, incomplètement contrôlés par un régime de corticostéroïdes en inhalation $\geq 1.000 \mu\text{g}$ et de bronchodilatateurs par inhalation, peut entraîner des améliorations des symptômes et de la fonction pulmonaire.

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