

A double-blind study of the efficacy of nedocromil sodium in the management of asthma in patients using high doses of bronchodilators

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The effects of nedocromil sodium were assessed in 110 patients with asthma who experienced asthma symptoms despite the use of high doses of inhaled bronchodilators. During the baseline period, antiinflammatory agents were not permitted, and patients were treated with inhaled β -agonists on an as-needed basis. Patients who required 12 or more puffs of albuterol and experienced continuing asthma symptoms for 7 of the 14 baseline days were randomized to treatment groups. Subjects received either nedocromil sodium (4 mg) or placebo four times a day for 10 weeks. Statistically significant ($p < 0.05$) between-treatment differences (weeks 3 to 10), favoring nedocromil sodium, were determined for the asthma summary score, daytime asthma severity, asthmatic cough, morning peak flow rates, reduction of as-needed bronchodilator use, physician's assessment of asthma severity, and patient and physician opinions of treatment effectiveness. By trial end (week 10), sleep difficulty caused by asthma decreased 29% in the nedocromil sodium group and 4% in the placebo group ($p = 0.006$). Nedocromil sodium was well tolerated and improved asthma control while reducing the inhaled bronchodilator load of these patients with moderately severe asthma. (J ALLERGY CLIN IMMUNOL 1994;94:473-81.)

Key words: Asthma, nedocromil sodium, albuterol, antiinflammatory, bronchodilator

Until recently, the pharmacotherapy of asthma in the United States has included β_2 bronchodilators, cromolyn sodium, corticosteroids, and theophylline. The clinical safety associated with several of the classical methods of asthma management has been challenged. Corticosteroids and theophylline treatment have both been reported to have deleterious clinical side effects,¹⁻¹⁰ and in some studies the regular use of inhaled β_2 -agonists has been associated with deterioration of asthma control.¹¹⁻¹³ Clearly, the need exists for safe phar-

Abbreviations used

FEV₁: Forced expiratory volume in 1 second
PEFR: Peak expiratory flow rate
prn: As needed
qid: Four times daily

macologic management of asthma with minimal side effects.

Nedocromil sodium is the disodium salt of a pyranoquinoline dicarboxylic acid, which was developed for management of the airway inflammation associated with asthma.¹⁴ Although its precise mechanisms of action remain under investigation, nedocromil sodium has been shown to be a potent modulator of many of the cellular components in the inflammatory response of asthma including eosinophils, neutrophils, macrophages, and mast cells.¹⁵

Clinically, nedocromil sodium has been shown to be effective in the treatment of mild to moderate asthma and to have no major side ef-

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Supported by Fisons Corporation, Rochester, New York. Received for publication Mar. 16, 1993; revised Feb. 10, 1994; accepted for publication Feb. 25, 1994.

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0091-6749/94 \$3.00 + 0 1/1/56077

fects.^{16, 17} In those studies in which patients' conditions were destabilized by the withdrawal of their maintenance bronchodilator regimen, nedocromil sodium adequately maintained control of asthma, and in many cases improved it.¹⁶⁻¹⁸ This is of particular interest for those patients who have limited success in managing their asthma with bronchodilators. In this study we evaluated whether nedocromil sodium could benefit patients with moderate asthma whose symptoms were not well controlled by high doses of inhaled bronchodilators.

METHODS

Trial design

The study was a 14-week double-blind, randomized, group comparative, placebo-controlled investigation (four centers). There was a 2-week run-in period, a 2-week baseline period, and a 10-week treatment period. All maintenance bronchodilators (theophylline, inhaled β_2 -agonists, oral β_2 -agonists) were stopped at the start of the baseline period; during this time, patients were only permitted to use inhaled β_2 -agonists on an as-needed (prn) basis. Entry into the treatment phase was dependent on demonstration of asthma symptoms (≥ 3 asthma summary score, further defined below), use of 12 or more puffs of albuterol per day for 7 of the 14 baseline days, and a forced expiratory volume in 1 second (FEV₁) of more than 40% of the predicted value with a 15% reversibility after β_2 -agonist use. Clinic visits were scheduled at the start of the run-in and baseline periods and at 2, 4, 6, and 10 weeks of treatment. The study was conducted in compliance with institutional review board and informed consent regulations.

Patient population

One hundred thirty-eight patients from four treatment centers were screened for entry into the study. They were diagnosed as having asthma, and before the study all patients used inhaled bronchodilators daily for management of their symptoms. The subjects were between 18 and 70 years of age, 47% were male, and approximately 92% of the patients had a documented history of atopy as determined by skin testing. Patients who had seasonal exacerbations of symptoms were excluded from the study.

Approximately 50% of the patients were using inhaled antiinflammatory therapy (inhaled corticosteroids, 30%; cromolyn sodium, 20%) before the start of the trial. These medications were withdrawn before the start of the run-in period (inhaled corticosteroids, 2 weeks before; cromolyn sodium, 4 weeks before), and the patients were switched to a sustained-release theophylline and/or inhaled or oral β_2 -adrenergic. Patients receiving immunotherapy were permitted to enter the study if their dose was stable for the preceding 6 months. Use of oral corticosteroids during the month before the study and intolerance to nedocromil sodium

or to the aerosol propellants were reasons for exclusion. Women of childbearing potential were entered into the study only if they were using safe and effective birth control measures. All subjects were able to complete daily diary cards properly and gave written informed consent.

Study medication

After the baseline period, the patients were randomly assigned to either the placebo or nedocromil sodium treatment group with computer-generated, sequentially coded study numbers. All subjects administered 2 inhalations from a metered dose inhaler four times daily (qid). The active test medication contained 2.0 mg nedocromil sodium (2.0 mg ex-valve, 1.75 mg ex-mouthpiece), 0.694 mg sorbitan trioleate, 81.604 mg dichlorodifluoromethane, and 54.402 mg dichlorotetrafluoroethane per actuation. The placebo had the same chemical composition without the nedocromil sodium.

Concomitant medications

During the run-in and baseline periods, patients were allowed to use albuterol and immediate-release theophylline (Somophyllin-T) on a prn basis for control of symptoms. During the treatment phase, the patients were instructed to take albuterol, up to 2 puffs six times per day, to control breakthrough symptoms. Immediate-release theophylline was provided as a backup treatment to be used only when the study treatment and 12 puffs of albuterol per day did not relieve symptoms of asthma.

Other permitted medications included topical nasal and prn oral decongestants, as well as topical corticosteroids for nasal use and nasal and ophthalmic cromolyn sodium. Oral β_2 -agonist bronchodilators, inhaled or oral corticosteroids for treatment of asthma, sustained-release theophylline, inhaled cromolyn sodium, and systemic antihistamines were not allowed.

Efficacy variables

The primary variable for efficacy of drug treatment was the symptom summary score, defined as the sum of the scores for daytime asthma severity and nighttime sleep difficulty. The primary time period was the final 8 weeks of treatment (weeks 3 to 10). Symptom severity scores were based on daily assessments by the patients and recorded on the diary card. Daytime asthma severity was recorded with a 5-point scale: 0 = no symptoms, 1 = asthma symptoms barely noticeable, 2 = asthma symptoms noticed from time to time but do not interfere with daily routine, 3 = asthma symptoms noticed often and interfere somewhat with daily routine, 4 = asthma symptoms present for most of day and radically change daily routine. Sleep difficulty was rated on a 3-point scale: 0 = slept well with no asthma, 1 = woke once because of asthma but was able to go back to sleep, and 2 = woke more than once because of asthma. Cough was reported on a 5-point scale (0 = no cough to 4 = very severe cough) similar to that used for

TABLE 1. Patient demographic characteristics

Characteristic	Placebo group (n = 56)	Nedocromil sodium group (n = 54)
Mean age (yr)	36.4	35.5
Age range (yr)	19-66	18-60
Male	26 (50%)	24 (44%)
Female	26 (50%)	31 (56%)
Asthma history		
Mean duration (yr)	18.5	19.3
Range (yr)	1-62	1.5-58
Disease history (% yes)		
Allergies	92.3	92.7
Family allergy history	71.2	70.9
Seasonal variation	73.1	80.0
Smoker	0	5.5
Former smoker	44.2	27.3
Previous asthma therapy during past year (% yes)		
Inhaled β -agonists	96.2	90.9
Oral β -agonists	17.3	21.8
Inhaled corticosteroids	30.8	30.9
Oral corticosteroids	23.1	27.3
Cromolyn sodium	23.1	23.6
Theophylline	69.2	70.9
Baseline lung function		
FEV ₁ (in liters)	2.59	2.58

daytime asthma severity. Patients also recorded twice daily (morning and evening) peak expiratory flow rates (PEFRs) on their diary cards and the daily prn use of albuterol and immediate-release theophylline. For the peak flow rates, the highest of three measurements obtained with an ASSESS peak flow meter (Health Scan Products, Cedar Grove, N.J.) was recorded. Measurements were done at the same time each day and not less than 4 hours after use of a bronchodilator.

Pulmonary function efficacy variables were FEV₁, PEFR, forced vital capacity, and forced expiratory flow. These were monitored at each of the seven clinic visits by recording the best of three consecutive measurements. Bronchodilators were withheld for 6 hours before pulmonary function testing. The primary pulmonary function variable was FEV₁ before bronchodilator use.

At each clinic visit the investigator examined the patient and reviewed the diary cards completed since the last visit and then rated the severity of the patient's asthma with a scale of 0 (no asthma) to 4 (very severe asthma). At the last clinic visit, both the physician and the patient expressed their opinion of the overall effectiveness of the study treatment with a 5-point scale (1 = very effective, 2 = moderately effective, 3 = slightly effective, 4 = no effect, 5 = made condition worse).

Any problems or new symptoms, whether attributable to the study treatment or not, were recorded at the clinic visits.

Statistical analysis

The two treatment groups were assessed for prestudy comparability with Fisher's exact test and two-sample *t* tests within centers, and the Mantel-Haenszel test and two-way (center by treatment) analyses of variance across centers for dichotomous and quantitative variables, respectively. Baseline assessment of asthma severity was analyzed with the Mann-Whitney U test within clinics and the Cochran-Mantel-Haenszel test to compare treatment groups across clinics.

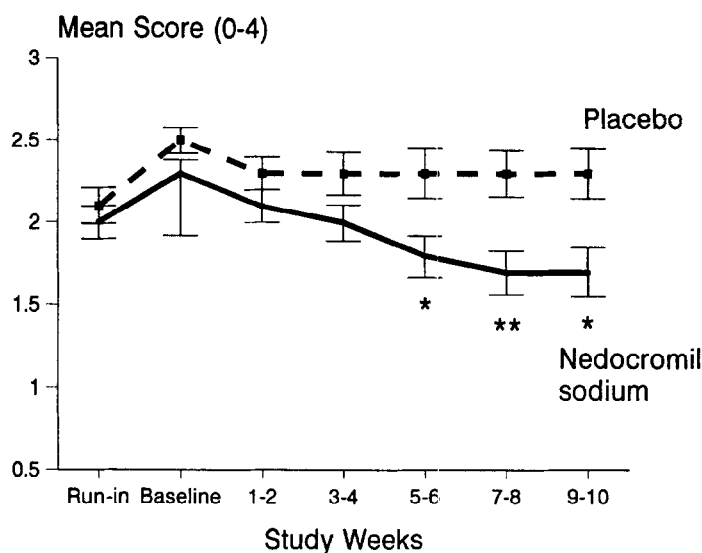
Between-treatment efficacy measures included the mean diary card symptom scores, morning and evening peak flow rates, concomitant prn medication use, and results of pulmonary function tests, which were analyzed by means of nonparametric analysis of covariance with baseline values as the covariate. Clinicians' assessment of asthma severity and clinicians' and patients' overall opinions of treatment effectiveness were analyzed with the Cochran-Mantel-Haenszel method. Comparisons between treatment period and baseline within each treatment group were based on the paired *t* test.

RESULT

Demographic data

One hundred thirty-eight patients were screened for entry into the study, and 110 patients were randomized to groups for treatment with either nedocromil sodium or placebo. As shown in

A. Daytime Asthma



B. Asthmatic Cough

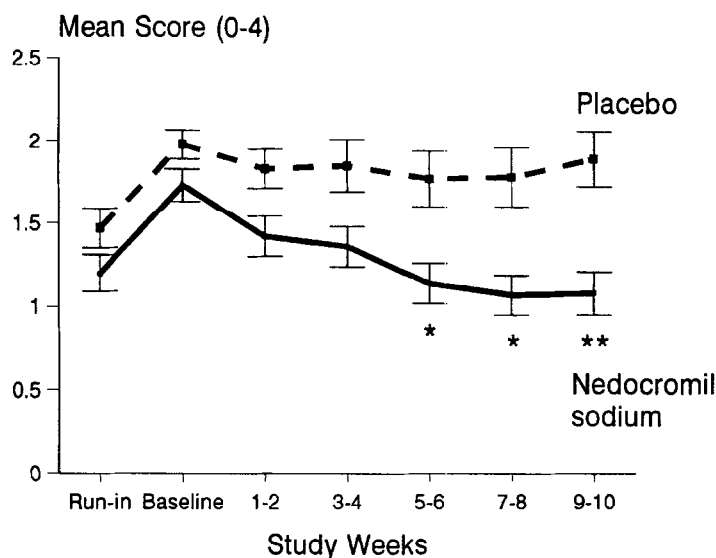


FIG. 1. A, Mean diary card scores for daytime asthma severity during the run-in, baseline, and treatment periods. **B,** Mean diary card scores for asthmatic cough. Both groups of patients demonstrated an exacerbation in asthma symptoms during the baseline period caused by the withdrawal of oral bronchodilators. The nedocromil sodium group is represented by the solid line (—); the placebo group is represented by the dashed line (---); error bars indicate $\pm$ standard error of the mean; * $p \leq 0.05$, ** $p \leq 0.01$.

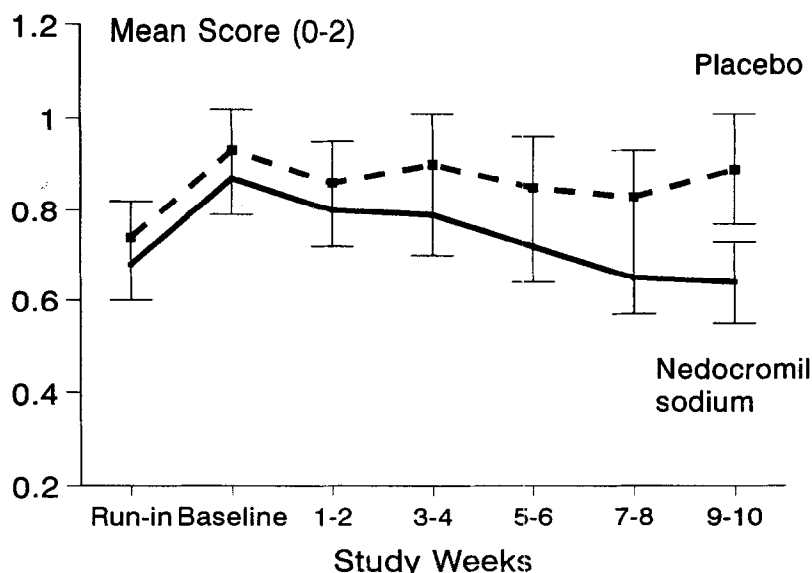
Table I, the results from the pretrial analysis showed the two treatment groups to be comparable for all demographic variables. Twelve patients (10 in the placebo group and 2 in the nedocromil sodium group) withdrew after randomization. Reasons for withdrawal in the nedocromil sodium group included noncompliance ($n = 1$) and study drug intolerance ($n = 1$). Patients in the placebo group withdrew because

of treatment failure ($n = 4$), lack of protocol compliance ($n = 3$), intercurrent illness ($n = 1$), intolerance to study drug ($n = 1$), and inability to meet entry criteria ($n = 1$).

Diary card scores

Analysis of the data from the diary cards indicated efficacy in favor of nedocromil sodium in the studied population. All between-group differ-

A. Sleep Difficulty Due to Asthma



B. Use of Concomitant Medication

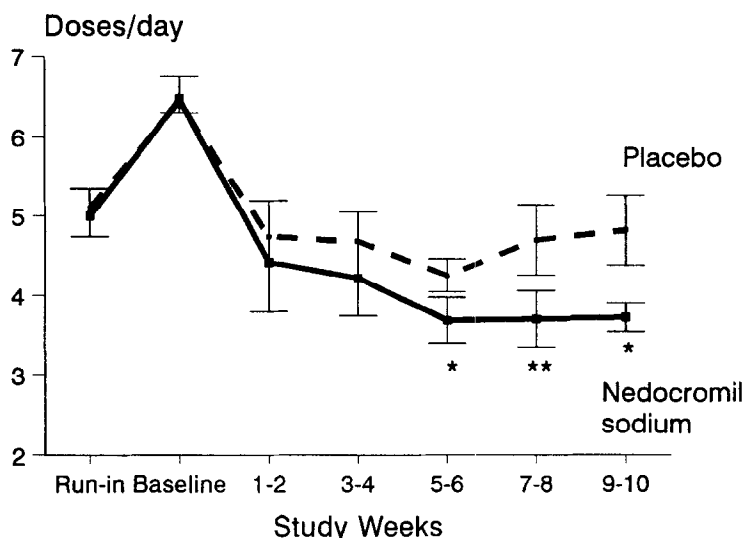


FIG. 2. **A,** Sleep disturbance caused by asthma. Withdrawal of oral bronchodilators during the baseline period resulted in an increase in sleep disturbance caused by asthma, which returned to run-in levels for patients treated with nedocromil sodium but not for control subjects treated with placebo. By the end of the trial (week 10), patients treated with nedocromil sodium demonstrated a significant decrease in sleep disturbance caused by asthma compared with baseline (data not shown, $p = 0.008$). **B,** Mean number of doses per day of prn bronchodilator medications (inhaled β_2 -agonist [2 puffs/dose] and immediate-release theophylline) used throughout the trial. Patients treated with nedocromil sodium demonstrated a significant decrease in use of rescue medication compared with patients with placebo. The nedocromil sodium group is represented by the solid line (—); the placebo group is represented by the dashed line (---); error bars indicate $\pm$ standard error of the mean; * $p \leq 0.05$, ** $p \leq 0.01$.

ences for diary card scores favored nedocromil sodium. Scores recorded for the asthma summary score (daytime asthma severity and sleep difficulty) were statistically significantly lower ($p = 0.01$) in the nedocromil sodium group for the

primary time period (treatment weeks 3 to 10). Specifically, statistically significant improvements in asthma control were observed in the nedocromil sodium group compared with the placebo group for daytime asthma severity and asthmatic

TABLE II. Patient diary card morning and evening PEFR

Treatment weeks	Peak flow rates (SEM)	
	Placebo	Nedocromil sodium
Morning		
Baseline (L/min)	396.1 (13.43)	376.5 (14.63)
Treatment weeks 3-10 (L/min)	392.6 (15.60)	392.6 (14.80)*
Evening		
Baseline (L/min)	434.3 (13.44)	412.3 (16.11)
Treatment weeks 3-10 (L/min)	425.3 (13.98)	429.3 (15.53)*

* $p \leq 0.01$ compared with baseline.

TABLE III. Percent predicted FEV₁ during the run-in, baseline, and treatment periods

Group	Run-in	Baseline	Treatment weeks			
			2	4	6	10
Nedocromil sodium	71	74	73	76	78	78
Placebo	66	72	74	72	75	75

cough (mean weeks 3 to 10: $p = 0.023$ and 0.007 , respectively). Individual between-group differences in favor of nedocromil sodium were evident during weeks 5 to 6, 7 to 8, and 9 to 10 (Fig. 1, *A* and *B*). Although scores for sleep difficulty caused by asthma steadily declined in the nedocromil sodium group, the between-group differences for the primary time period did not reach statistical significance ($p = 0.07$, mean of weeks 3 to 10). However, by trial end (week 10), patients in the nedocromil sodium group reported significant decreases in sleep disturbance compared with those in the placebo group ($p = 0.006$) (Fig. 2, *A*). Furthermore, compared with baseline, only the nedocromil sodium-treated group had a significant reduction in sleep disturbance throughout the primary time period (treatment weeks 3 to 10, $p = 0.008$).

During the 10-week treatment period, peak flow rates steadily increased in the nedocromil sodium group but not in the placebo group. Compared with baseline values, patients treated with nedocromil sodium showed statistically significant increases in both morning ($p = 0.001$) and evening ($p = 0.003$) peak flow rates during the primary treatment period (Table II). The improvement in diary card variables for the subjects treated with nedocromil sodium occurred despite significantly less use of rescue concomitant medications (Fig. 2, *B*). Compared with the placebo group, patients in the nedocromil sodium group showed a statistically significant reduction in their prn bronchodilator

intake for treatment weeks 5 to 6 ($p = 0.022$), 7 to 8 ($p = 0.016$), and 9 to 10 ($p = 0.042$), as well as for the primary time period ($p = 0.025$, weeks 3 to 10). At trial end, the use of prn bronchodilators decreased an average of 41% in the nedocromil sodium group and 28% in the placebo-treated control group compared with baseline.

Pulmonary function tests

The results of the pulmonary function tests showed no significant differences between the treatment groups during the course of the study. The FEV₁ data were transformed to percent predicted values, and results are given in Table III. During the baseline period, the mean FEV₁ percent predicted values were 74% and 72% for the nedocromil sodium and placebo groups, respectively. After 10 weeks of treatment, the mean FEV₁ percent predicted values were 78% for the nedocromil sodium group and 75% for the placebo group. Patient distribution of the percent predicted FEV₁ values is illustrated in Fig. 3. Interestingly, after 10 weeks of nedocromil sodium treatment, there was an increase in the number of patients whose percent predicted FEV₁ was in the 80% to 100% range.

Clinical assessment

Results of the analysis of the physicians' assessments of the patients' asthma severity revealed lower scores for the nedocromil sodium group at visits 5, 6, and 7. The difference between the

scores of the treatment groups was statistically significant in favor of nedocromil sodium after 10 weeks of treatment ($p = 0.03$; mean week 10: nedocromil sodium = 1.78, placebo = 2.29).

Final overall opinions of treatment expressed by both the physicians and the patients confirmed the results of the efficacy variables. Both the physicians and patients strongly favored nedocromil sodium over placebo ($p \leq 0.0001$).

Adverse events

Forty-one (74.5%) of the patients treated with nedocromil sodium and 42 (81%) of those treated with placebo reported at least one adverse event during the course of treatment. Of these, 41% of the patients receiving nedocromil sodium and 39% of the patients receiving placebo reported at least one event that was judged to be related to the test medication. Those adverse events judged to be related to test medication, which occurred in more than one patient ($\geq 3\%$) are shown in Table IV. Bronchospasm and dyspnea were the adverse events most commonly reported in the placebo group, and unpleasant taste was the most common event in the nedocromil sodium group. Lastly, in this study the percentage of patients treated with nedocromil sodium reporting unpleasant taste was considerably higher than in other reported clinical trials: approximately 29% compared with 12% for clinical trials worldwide.¹⁹ However, no patient withdrew because of this transient unpleasant taste. The possibility that unpleasant taste might have an effect on treatment compliance, and consequently treatment efficacy, was investigated. Specifically, patients were divided into two subgroups on the basis of their ability to taste nedocromil sodium: tasters and nontasters. Patient diary card variables were analyzed with one-way analysis of covariance for treatment weeks 3 to 10. The results from this subanalysis demonstrated that there was no significant difference in asthma symptom scores of PEF data between the tasters ($n = 16$) and the nontasters ($n = 39$) among the patients treated with nedocromil sodium (Table V).

DISCUSSION

Currently, many patients with mild to moderate asthma rely on inhaled β_2 -agonists to control their symptoms. Such therapy has come under scrutiny in recent years because some studies have suggested that regular use of β_2 -agonists may be associated with deterioration of asthma control,^{11, 12} and in excessive dosages, with increases

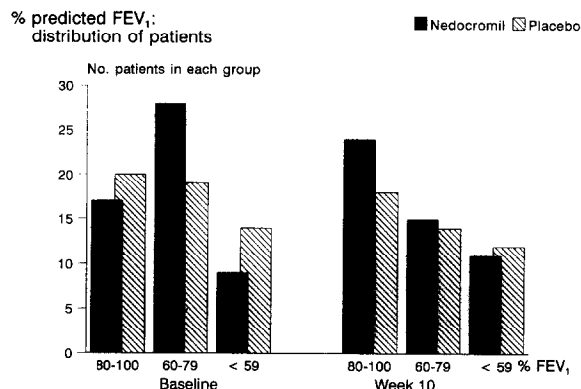


FIG. 3. Distribution of patients based on percent predicted value of FEV₁. During the baseline period and week 10, there was little change in the severity of asthma in patients treated with placebo as determined by distribution of the number of patients in each of three categories of FEV₁. However, patients in the nedocromil sodium group demonstrated a shift in asthma severity. Specifically, during the baseline period, there was a predominance of patients in the moderate asthma category (60% to 79% of predicted value). After 10 weeks of treatment, there was a shift from moderate to mild asthma as the number of patients with FEV₁ between 80% and 100% of predicted value increased.

in morbidity and mortality rates.^{12, 20} Moreover, recent data suggest that regular use of β_2 -agonists, at least in conjunction with allergen exposure, might be "proinflammatory."²¹

Current guidelines for asthma management stress the need to provide combination therapy with an antiinflammatory agent and to avoid single entity bronchodilator use in patients, even if their asthma is relatively mild.^{22, 23} The results from this study show that nedocromil sodium (4 mg) qid permits reduction in bronchodilator use and safely reduces the major symptoms of asthma in patients with mild to moderate asthma whose disease was not well-controlled by high doses of bronchodilators (specifically, inhaled β_2 -agonist: ≥ 12 puffs/day). For both treatment groups, symptom scores increased during the baseline period. During the treatment phase, the diary scores for patients in the placebo group remained elevated at the baseline level. In contrast, all diary symptom scores for the patients treated with nedocromil sodium decreased. These improvements occurred despite significantly less bronchodilator use compared with patients treated with placebo.

Other clinical studies have demonstrated that nedocromil sodium improves symptom control and decreases the bronchodilator dependence of pa-

TABLE IV. Adverse events judged to be treatment-related

Adverse event	Nedocromil sodium group	Placebo group
Unpleasant taste	16 (29%)*	1 (2%)
Pharyngitis	3 (5%)	1 (2%)
Bronchospasm	2 (4%)	6 (11%)
Dyspnea	2 (4%)	5 (9%)
Chest pain	2 (4%)	4 (7%)
Insomnia	2 (4%)	1 (2%)
Coughing	1 (2%)	3 (6%)
Dizziness	0	2 (4%)
Pruritus	0	2 (4%)

* $p \leq 0.05$ compared with placebo.

TABLE V. Analysis of patient diary card data based on subgroups: Tasters versus nontasters (during primary time period)

	Tasters ($n = 16$)	Nontasters ($n = 39$)	p Value
Asthma summary score	2.59	2.48	0.79
Daytime asthma severity score	2.02	1.77	0.43
Sleep difficulty caused by asthma score	0.66	0.70	0.81
Cough severity score	1.15	1.16	0.98
PEFR (L/min)			
Morning	398.9	392.3	0.64
Evening	442.9	425.9	0.25

tients with mild to moderate asthma.¹⁶⁻¹⁹ However, this trial differs from prior studies in that the use of inhaled β_2 -agonists during the baseline period was very high (≥ 12 puffs for 7 of 14 baseline days). Interestingly, during the treatment phase, both treatment groups reduced their use of inhaled albuterol and immediate-release theophylline. However, relative to baseline, patients treated with nedocromil sodium reported a statistically significant larger decrease over those treated with placebo.

Unlike the diary card scores, the statistical analysis of the pulmonary function data indicated comparability between the treatment groups. This is in contrast to other studies showing that nedocromil sodium (4 mg) improves lung function parameters when administered in dosing schedules of either two times daily or qid.¹⁶⁻¹⁹ One possible explanation is the high availability of the potent short-acting inhaled bronchodilator, which was permitted up to a maximum of 12 puffs daily. However, when the percent predicted FEV₁ values are examined, a difference between groups is noted in patient distribution on the basis of disease severity. Over the course of the 10-week trial, the placebo group showed little change in the distribution of number of patients in each group of FEV₁ percent

predicted values: 80% to 100% (mild asthma), 79% to 60% (moderate asthma), 59% or less (severe asthma). The nedocromil sodium group demonstrated a shift in patient distribution with more patients in the 80% to 100% predicted range after 10 weeks of treatment.

In addition to nedocromil sodium, other inhaled antiinflammatory agents may be used to treat asthma in patients requiring more than occasional bronchodilator therapy. Well-controlled clinical trials have demonstrated the comparability of nedocromil sodium (4 mg) and low doses of inhaled beclomethasone dipropionate (100 μ g) qid in the treatment of mild to moderate asthma.²⁴⁻²⁶ Corticosteroids are excellent antiinflammatory agents and are currently indicated for the treatment of moderate or severe asthma; however, the long-term implications of the possible systemic effects of inhaled corticosteroids have yet to be determined. Studies implicating high doses of maintenance bronchodilators in the loss of asthma control raise important concerns regarding treatment strategies for many patients with asthma. An effective nonsteroidal antiinflammatory agent with no significant adverse effects is a useful first-step maintenance therapy for the treatment of mild to moderate asthma. The

results of this study suggest that nedocromil sodium (4 mg qid) is a safe primary antiinflammatory therapy for patients with mild to moderate asthma who use high doses of bronchodilators.

We thank Judith Rosen Farrar, PhD, and Starr H. Pearlman, PhD, for their technical assistance in preparation of this manuscript.

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