

Nedocromil sodium is rapidly effective in the therapy of seasonal allergic rhinitis

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Background: Nedocromil sodium has proven to be efficacious in prophylactic and long-term therapy for the treatment of seasonal allergic rhinitis. We examined the speed of onset of intranasal nedocromil sodium (1%) for relief of symptoms due to ragweed allergic rhinitis.

Methods: In a double-blind, placebo-controlled trial, 104 patients received either nedocromil sodium or placebo four times daily. Patients spent 10 hours per day for 2 consecutive days in Iowa City Park during the peak of ragweed season. Only patients who had significant symptoms during 3 hourly baseline assessments received drug. Symptom scores for stuffy nose, runny nose, itchy nose, and sneezing and global symptom summary scores were recorded at 19 hourly time points during the 2 days. In the evening patients recorded symptom scores for the postexposure period.

Results: In comparison with placebo, nedocromil significantly improved rhinitis symptoms as evidenced by lower symptom summary scores within 2 hours ($p = 0.016$). Further, this reduction in rhinitis symptoms was maintained throughout the 2-day pollen exposure period. After patients left the study site, postexposure symptom summary scores were also significantly lower in patients treated with nedocromil compared with those treated with placebo ($p < 0.007$).

Conclusions: Nedocromil significantly relieved preexisting seasonal allergic rhinitis symptoms during peak pollen exposures within 2 hours of the first dose, and the therapeutic benefits were maintained on a dosing regimen of four times a day. (*J ALLERGY CLIN IMMUNOL* 1993;91:997-1004.)

Key words: Nedocromil sodium, allergic rhinitis, ragweed pollen

Allergic rhinitis is the clinical syndrome triggered by the IgE-dependent release of mediators from nasal mast cells and basophils after inhalation of airborne allergens. The rapid release of mediators such as histamine, prostaglandins, and leukotrienes results in an immediate or early-phase reaction. In addition to this early-phase reaction, a late-phase response, which is associated with the influx and activation of eosinophils, basophils, and neutrophils, often results. It has been shown that both the immediate and late clinical responses to antigen strongly correlate with mediator release.¹ Thus therapeutic control of the symptoms of allergic rhinitis places empha-

Abbreviations used

IgE: Immunoglobulin E
PGD₂: Prostaglandin D₂

sis on the prevention of mediator release and the subsequent inflammatory response.

Nedocromil sodium is the first of a new generation of chemical compounds, the pyranoquinoline dicarboxylic acids. Nedocromil has been shown to act on a wide variety of inflammatory cells associated with both the early and late inflammatory responses.² In addition to its ability to stabilize resident mast cells, it has been shown to prevent the influx and activation of both neutrophils and eosinophils.³⁻⁷ Nedocromil sodium has also been shown to prevent nasal obstruction, rhinorrhea, and sneezing when given before acute allergen exposure in ragweed-sensitive individuals.⁸ Moreover, nedocromil has proven to be efficacious in the treatment of patients with symptomatic allergic rhinitis.⁹⁻¹³

The previously mentioned clinical trials demonstrate the prophylactic benefit of nedocromil so-

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TABLE I. Study design

Parameter	Day 1 (08/25/90)	Day 2 (08/26/90)
Baseline nasal assessment (hourly)	X (7:00-9:00 AM)	NA
Randomization to treatment*	X (9:00 AM)	NA
Drug administered (9:00 AM, 1:00 PM, 5:00 PM, 9:00 PM)	X	X
Hourly symptom scores	X (10:00 AM-10:00 PM)	X (7:00 AM-10:00 PM)
Hours in park (7:00 AM-5:00 PM)	X	X
Hours at home (6:00 PM-6:00 AM)	X	X
Sleep disturbance assessment (10:00 PM-6:00 AM)	X	X

NA, Not applicable.

*Subjects were randomized to either nedocromil sodium or placebo treatment if total symptom scores were ≥ 13 during baseline nasal assessment period on day 1. See Table II for patient assessment scoring scales.

dium in long-term therapy for seasonal allergic rhinitis. However, there are no data that examine the onset of therapeutic benefit after patients begin to experience significant symptoms of seasonal allergic rhinitis. This study therefore attempted to evaluate the length of time between initiation of therapy with nedocromil sodium 1% nasal solution given four times a day and the onset of statistically significant benefit in the treatment of ragweed-induced allergic rhinitis. In a double-blind, placebo-controlled trial subjects were exposed to naturally occurring ragweed pollen during a 2-day period, and hourly symptom scores were recorded.

METHODS

Study objectives

The study objectives were to assess: (1) the speed of onset, (2) efficacy, and (3) safety of nedocromil sodium 1% nasal solution versus placebo in the acute therapy of ragweed-induced allergic rhinitis.

Subject selection

Subjects between the ages of 12 and 65 years with ragweed pollinosis were recruited from the University of Iowa Allergy-Immunology Clinic, from lists of subjects who had participated in previous allergic rhinitis studies and through advertisements in the local media. The diagnosis of allergic rhinitis was confirmed by at least a 2-year history of ragweed-induced allergic rhinitis symptoms and positive results of prick or intra-

dermal skin tests to short ragweed (obtained from Greer Laboratories, Inc., Lenoir, N.C.).

Those subjects who had moderate-to-severe asthma, perennial rhinitis with little or no seasonal flare-up, sinusitis, polyposis, deviated nasal septum, rhinitis medicamentosa, or poor general health as determined by history or physical examination were excluded. Female subjects were required to be of nonchild-bearing potential. Subjects who were receiving maintenance immunotherapy were allowed to participate if they had not started immunotherapy since the last ragweed season or if they had not stopped or altered their doses within 3 months of the study period. Each subject was informed of potential risks and benefits of the study in accordance with the Human Subjects Review Committee at the University of Iowa, and a written informed consent agreement was signed by the patient and the investigators.

Study design

A summary of the study design appears in Table I. Subjects spent 2 consecutive days (August 25 and 26, 1990) from 7:00 AM to 5:00 PM in an outdoor park during the peak of ragweed season. Before the study began, subjects demonstrated a positive ragweed skin test and underwent a complete history and physical examination. Those who met all entry criteria as listed above were enrolled in the study and instructed to report to the park at 6:30 AM on August 25, 1990. They were told to discontinue all rhinitis medications after August 11, 1990, except for short-acting antihistamines and decongestants, which were allowed up until 72 hours before they reported to the park. Inhaled β_2 -agonists were

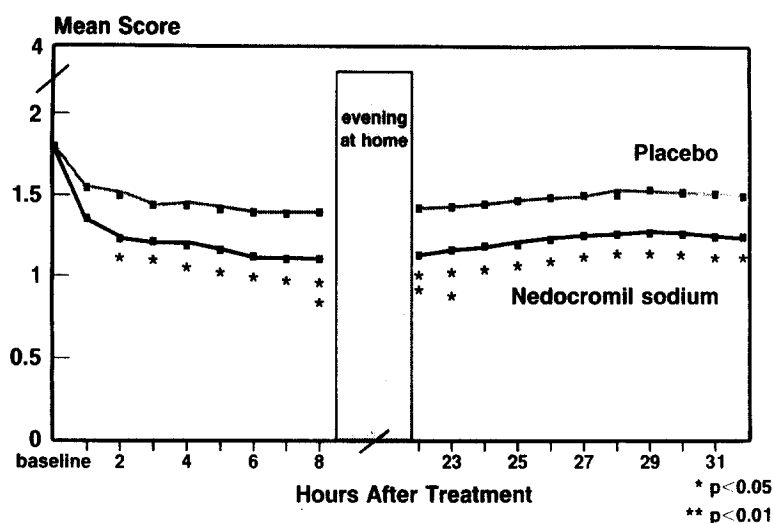


FIG. 1. Cumulative symptom summary scores at the park. The mean cumulative symptom summary score demonstrated that within 2 hours of the first treatment dose, patients in the nedocromil sodium group had fewer rhinitis symptoms as compared with patients in the placebo group. Therapeutic benefits were maintained throughout the study.

allowed for relief of mild asthma symptoms. On arrival at the park, patients were screened to determine whether they remained eligible (e.g., no evidence of fever or acute upper respiratory infection and no use of prescribed medications).

During the 2-day study period, hourly symptom scores of stuffy nose, runny nose, itchy nose, and sneezing were recorded on a scale of 0 to 4 from 7:00 AM to 10:00 PM. Additional assessments were made of sleep disturbance due to rhinitis symptoms (scale, 0 to 2) and an overall opinion of the medication's effectiveness (scale, 1 to 5) (Table II). Hourly pollen counts at the study site and daily pollen counts at the University of Iowa were done with the Rotorod method.

Subjects recorded symptoms at 7:00, 8:00, and 9:00 AM on day 1. Only subjects who had significant symptoms as evidenced by a total symptom score of 13 during this 3-hour baseline period were randomized to treatment. Each subject was then assigned study medication sequentially according to a computer-generated randomization code. After instruction was given in the use of the nasal spray, patients received one spray in each nostril of nedocromil sodium or placebo at 9:00 AM. Patients remained in the park and completed symptom score cards hourly until 5:00 PM. Medication was again taken at 1:00 PM and 5:00 PM. After 5:00 PM, the patients returned to their homes where they continued to complete hourly symptom cards until 10:00 PM. At 9:00 PM, the fourth blinded dose of medication was taken. On arising on day 2, subjects recorded a sleep disturbance questionnaire in relation to rhinitis symptoms. At 7:00 AM they returned to the park where they once again completed hourly symptom score cards until 5:00 PM. Medication was taken at 9:00 AM, 1:00 PM,

TABLE II. Patient assessment scoring

1. Symptom scores (stuffy nose, runny nose, itchy nose, sneezing)
 - 0 = Symptom absence
 - 1 = Symptom barely noticeable
 - 2 = Symptom caused some discomfort
 - 3 = Symptom caused enough discomfort to interfere a little with activities
 - 4 = Symptom present for most of the day; caused enough discomfort to interfere greatly with activities
2. Sleep disturbance
 - 0 = Slept undisturbed by nose symptoms
 - 1 = Felt stuffy on retiring to bed or awakened once by nose symptoms
 - 2 = Awakened several times by nose symptoms
3. Treatment efficacy
 - 1 = 100%, Fully controlled symptoms
 - 2 = 75%, Mostly controlled symptoms
 - 3 = 50%, Fairly controlled symptoms
 - 4 = 25%, Poorly controlled symptoms
 - 5 = 0%, No control of symptoms

and 5:00 PM. At 5:00 PM, patients returned to their homes and continued to complete symptom scores until 10:00 PM. The final dose of medication was taken at 9:00 PM. On the next morning, subjects completed a questionnaire regarding sleep disturbance due to rhinitis symptoms. Within 3 days they returned to the clinic and were asked to rate their opinion of the study medication's overall effectiveness. At each hourly time period at the park and after completion of evening symptom scores, subjects were asked whether they had

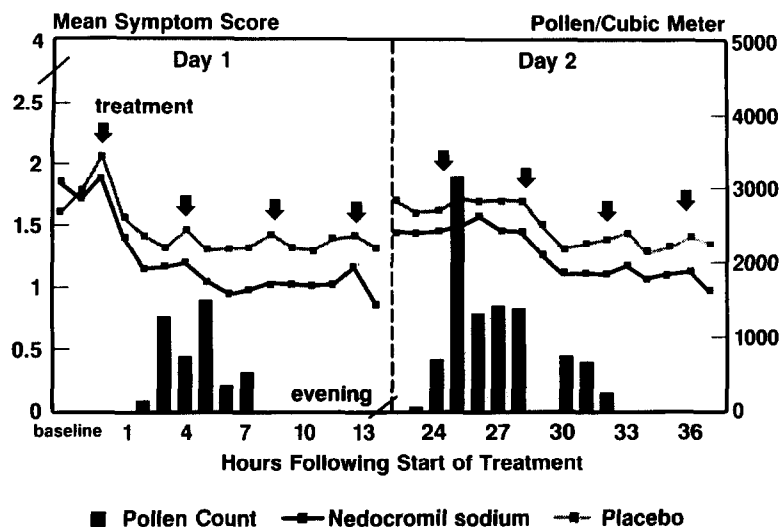


FIG. 2. Mean symptom summary scores throughout the study. Mean symptom scores by the hour showed that patients treated with nedocromil sodium 1% nasal solution had an improvement in nasal symptoms as early as the second hour of treatment and remained improved throughout the 2-day study. Arrows indicate drug administration. Patients were in the park during the baseline period and from hours 1 through 8 and 22 through 32.

any adverse experiences. Information collected included a description of the event, date and time of onset, duration, severity, assessment of relationship of the event to study drug, action taken, probable contributory patterns, and outcome. Any adverse events reported were closely followed up until they were resolved.

Statistical analysis

The treatment groups were assessed for pretrial comparability. Dichotomous variables were compared by Fisher's exact test, ordinal variables by Wilcoxin rank-sum tests, and continuous variables by two-sample *t* tests.

In assessment of the primary objective of onset of action, the efficacy variable was the symptom summary score defined as the mean of scores for sneezing, itchy nose, runny nose, and stuffy nose. The assessments for this objective were only those recorded under closely controlled conditions at the park (from 7:00 AM to 5:00 PM). Patients assessed symptoms at three time points before treatment (baseline) and at 19 time points while at the park. For each patient an average baseline score was computed from the 7:00, 8:00, and 9:00 AM assessments. For the assessments during treatment at the park a mean cumulative symptom summary score was computed hourly, and it included all previous determinations. Thus 19 separate variables defined as the patient's average symptom summary score were computed.

With analysis of covariance, the baseline score was compared with each of the 19 onset-of-action variables. When statistical significance was achieved, a claim for

onset of action was to be made for that particular time point only when all assessments after that point were also statistically significant at the $\alpha = 0.05$ level; that is, when differences between the treatment and placebo groups became statistically significant, they were required to remain so.

Analysis of covariance was used to assess the effects of nedocromil sodium after patients left the park. The symptom summary scores were averaged across all 10 assessments performed at home (hourly scores from 6:00 PM to 10:00 PM on days 1 and 2) and compared with the average baseline symptoms summary score. Sleep disturbance due to rhinitis symptoms and the patient's overall opinion of the medication's effectiveness were analyzed by the Wilcoxin rank-sum test.

Subjects who withdrew for reasons unrelated to treatment failure were used in the statistical analysis to the point of withdrawal, provided that they had recorded enough data to warrant analysis. For the primary onset-of-action analysis, this was defined as the presence of recorded scores for at least half of the assessments for each variable.

RESULTS

Subjects

One hundred fifty-four subjects were screened and met criteria for entry into the study. However, 45 were withdrawn before randomization because of insufficient baseline symptoms or failure to report to the study site on day 1. A total of 109 subjects were randomized to treatment, 54 to the nedocromil sodium group and 55 to the placebo

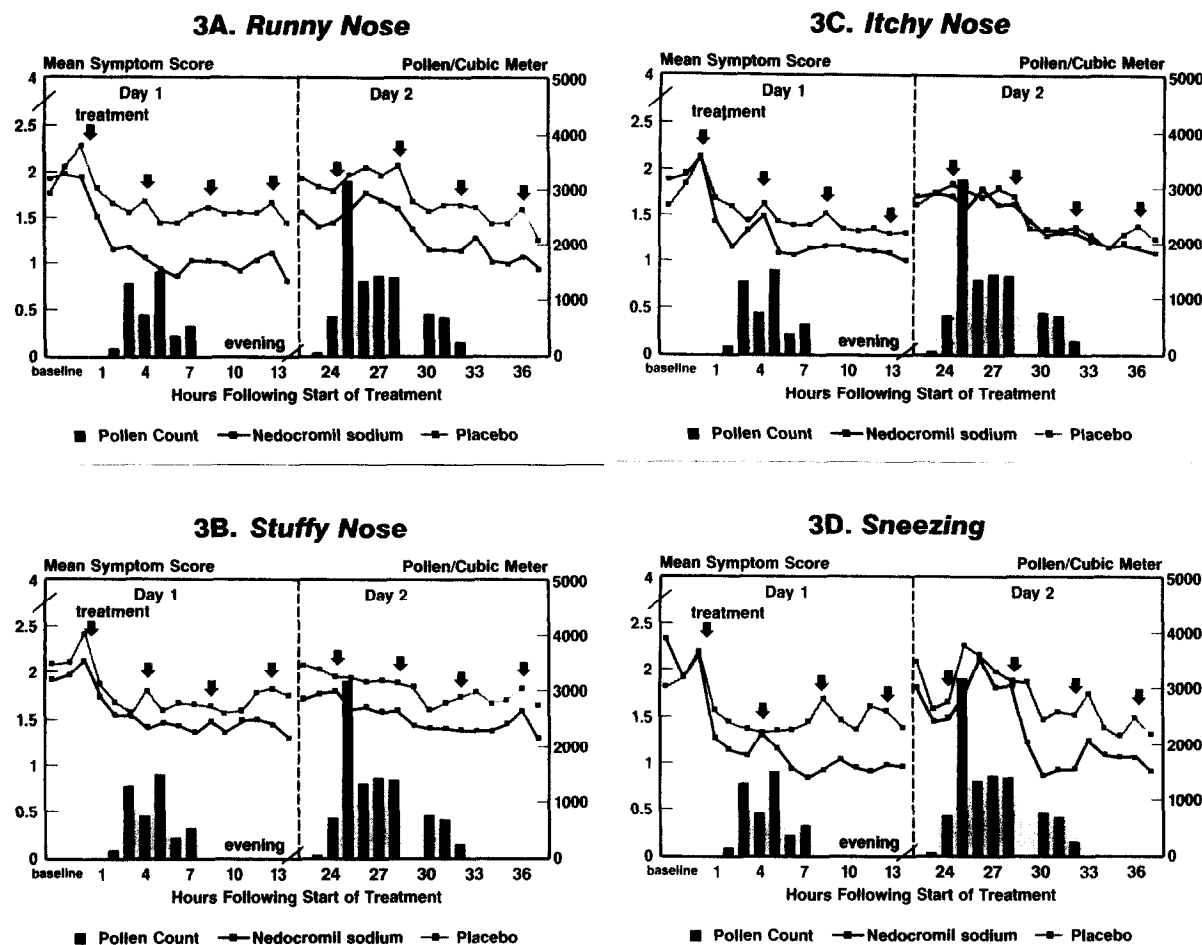


FIG. 3. Mean individual symptom scores throughout the study. Mean individual symptom scores by the hour showed that patients treated with nedocromil sodium had improved mean hourly symptoms for (3A) runny nose, (3B) stuffy nose, (3C) itchy nose, and (3D) sneezing. The most dramatic improvements were noted in the nedocromil sodium group for both runny nose and sneezing. Arrows denote drug dosing.

group. Of these, 103 subjects completed the study and were fully evaluated (52 received nedocromil sodium and 51 received placebo). Among the six subjects that were withdrawn after randomization, two received active drug and four received placebo. In the active treatment group, one patient withdrew because of exacerbation of asthma symptoms and one because of a family emergency. In the placebo group reasons for withdrawal included development of concomitant illness and protocol violations, which were generally for personal reasons.

Pretrial treatment group comparability

The treatment groups were comparable with regard to mean age (26.3 years vs 29.7 years for active vs placebo groups), sex (91% vs 87% male subjects for active vs placebo groups), and physi-

cal characteristics (height, weight, and vital signs). Patients had a duration of seasonal allergic rhinitis for an average of 15.0 years in the active treatment group and 16.9 years in the placebo treatment group. All patients experienced a seasonal increase in rhinitis symptoms corresponding to the ragweed pollen season and had used medication for rhinitis symptoms during the previous ragweed season. Rhinitis symptoms during the previous season and baseline nasal symptoms recorded on the patient score cards were comparable between the active- and placebo-treated groups.

Onset of action

Fig. 1 shows the mean baseline and the mean cumulative symptom summary scores for assessments 1 through 19 at the park. The results indicate

TABLE III. Postexposure challenge and sleep disturbance due to rhinitis

Variable	Mean values*		<i>p</i> Value
	Active	Placebo	
Summary score - after pollen challenge (at home)	1.06	1.36	0.0066
Sleep disturbance due to rhinitis	0.60	0.71	0.2461

*See Table II for definition of scoring system.

that a claim for onset of action of 2 hours after the first dose could be made for nedocromil sodium. Statistical significance between nedocromil- and placebo-treated groups was achieved after 2 hours of treatment ($p = 0.016$) and was sustained through the 2 days at the park ($p = 0.009$ to 0.036). Fig. 2 shows the mean unadjusted hourly symptom summary scores for each treatment group, both at the park and at home. Also displayed are the hourly pollen counts (pollen grains per cubic meter). At all time points the nedocromil-sodium-treated group exhibited lower mean symptom summary scores.

Duration of action

Fig. 3 displays the mean unadjusted hourly symptom scores for runny nose (3A), stuffy nose (3B), itchy nose (3C), and sneezing (3D), both while in the park and at home. Also displayed are the hourly pollen counts. For all symptoms except itchy nose on day 2, the nedocromil-sodium-treated group had lower mean scores, which indicates less severity throughout the 2-day study. Stuffy nose was scored the highest, followed by runny nose, itchy nose, and sneezing. Nedocromil sodium appeared to have provided the greatest relief of the runny nose symptom.

The results of the statistical analysis for the mean symptom summary scores recorded at home are also in favor of nedocromil sodium ($p = 0.0066$) (Table III). Although the sleep disturbance due to rhinitis symptoms favored the active treatment group, it was not statistically significant ($p = 0.246$) (Table III). There was not a statistically significant difference between treatments according to the patients' final opinion of treatment effectiveness ($p = 0.4793$). Sixty percent (32 of 53) of the subjects in the active group indicated that the study medication fairly, mostly, or fully controlled their symptoms as compared with 52% (28 of 54) of the placebo group.

Safety analysis

Ten (19%) of the patients in the active group and three (5%) of the patients in the placebo group reported at least one adverse event during the course of treatment. "Headache," the most commonly reported adverse event, was reported by three patients (6%) in the active group and by one patient (2%) in the placebo group. Those symptoms judged to be possibly related to the study medication were pharyngitis (two patients), stomatitis (one patient), and nose burning (one patient). Overall, however, very few adverse events were reported and none were considered serious.

DISCUSSION

The study design was chosen to provide the appropriate environment in which to examine the onset of action of a 1% nedocromil sodium nasal solution in the management of symptoms of seasonal allergic rhinitis. Subjects were naturally exposed to ragweed pollen for 10 hours a day on 2 consecutive days without escape into air-conditioning or use of concomitant medications. The pollen counts were somewhat reduced during the baseline period as a result of early morning rainfall but were still significant. Moreover, the restrictions placed on the use of rhinitis medications before the commencement of the study increased the likelihood that subjects would arrive at the park demonstrating significant symptoms. The collection of hourly symptom score cards and close monitoring of medication administration guaranteed compliance.

Within 2 hours of the first dose of medication, the nedocromil-sodium-treated group showed a statistically significant reduction in nasal symptoms due to ragweed-induced allergic rhinitis compared with the placebo-treated group ($p = 0.016$); this reduction was maintained throughout the 2 days of the study. An increase in symptoms was observed in both groups on return to the park on day 2. This was most likely due to the study design whereby patients were subjected to what was a 3-hour rechallenge on day 2 before they received medication at 9:00 AM. It might have been more appropriate to have administered the first dose of medication at 7:00 AM rather than at 9:00 AM on day 2. Nonetheless, it is important to note that despite the dramatic rise in pollen on day 2 seen between 9:00 and 10:00 AM (>3000 grains per cubic meter), the nedocromil-sodium-treated group continued to demonstrate a therapeutic benefit as compared with the placebo-treated group.

Consideration of individual symptom scores showed stuffy nose to be the most prominent symptom, followed by runny nose, itchy nose, and sneezing. In comparison with the placebo-treated group, the nedocromil-sodium-treated group had lower mean symptom scores for all symptoms except for itchy nose on day 2. Nedocromil sodium appeared to have the greatest benefit for runny nose. Although scores favored the nedocromil-sodium-treated group, there was not a statistically significant difference in sleep disturbance due to rhinitis symptoms.

The patients' overall opinion of the medication's effectiveness was intended as a comparison between pretreatment and posttreatment symptoms while in the park. In retrospect, we realize that the information gathered was probably not appropriate to make this assessment. Within 3 days of the study's completion, subjects were asked, "In your opinion, since the last visit how effective was the study treatment in controlling your symptoms?" Phrasing the question in this manner led the patients to compare their symptoms after 2 days in an outdoor environment with the degree of relief experienced after they returned to air-conditioning and resumed use of a variety of pharmacologic measures. It would have been more appropriate to collect this assessment at the end of study day 2. This question design error likely accounted for the overall patient opinion, which did not significantly favor the study medication.

Long-term studies have documented the good safety profile of nedocromil sodium.^{9, 10, 13, 14} The minimal adverse events reported in the treatment group supports the safety of nedocromil sodium nasal solution. Indeed, no adverse events in the active group were judged to be sufficiently serious to warrant patient withdrawal from the study.

The physiologic mechanisms of allergic rhinitis are complex and not fully understood. During pollen season the number of nasal mast cells has been shown to increase¹⁵ and to correlate with symptom severity.^{15, 16} The initial response to antigen appears to be related primarily to mast cell activation and subsequent mediator release, followed by an inflammatory process that involves an influx of eosinophils, basophils, and neutrophils and a different pattern of mediator release.¹⁷ Therapeutic control of the disease therefore places emphasis on preventive measures, which may inhibit these processes.

Current topical therapy for allergic rhinitis includes administration of cromolyn sodium and

intranasal steroids. Pretreatment with cromolyn 3 hours before allergen exposure has been shown to inhibit both the early- and late-phase allergic reactions. Although therapeutic benefit of cromolyn can be achieved during allergen exposure, the best results are seen when therapy is initiated before allergen exposure.¹⁸ Topical steroids are highly effective in controlling nasal inflammation associated with the late-phase response,^{19, 20} but several days of therapy before allergen exposure may be required for complete control.²¹ Therefore patients who are already highly symptomatic may require the addition of an antihistamine-decongestant combination during the first few days of treatment. Ideally, it would be preferable to have a potent therapeutic agent that inhibits both the early- and late-phase responses, which could provide substantial relief within hours rather than days. Our data suggest that nedocromil might be such an agent.

Numerous *in vitro* and *in vivo* studies have been conducted in an attempt to determine the precise mechanism or mechanisms of action responsible for nedocromil sodium's ability to relieve the symptoms of seasonal allergic rhinitis. When patients were treated with nedocromil sodium before allergen exposure, inhibition of mast cell accumulation has been demonstrated.²² When compared with cromolyn sodium, nedocromil sodium was shown to be more effective in inhibiting the release of histamine, leukotriene C₄ and prostaglandin D₂ (PGD₂) from mast cells derived from monkey airways.²³ Kaulbach et al.²⁴ studied the immediate effects of nedocromil sodium on the pattern of nasal symptoms and secretions after allergen challenge. The nasal lavage level of PGD₂, a marker of mast cell degranulation, correlated with the severity of symptom scores. Although there was a trend in favor of nedocromil sodium, these investigators found no difference in PGD₂ nasal lavage levels between nedocromil sodium and placebo treatment groups. Perhaps the artificial nature of the challenge itself did not mimic natural allergen exposure. The rapid therapeutic effect that nedocromil sodium demonstrated in our study and the significant reduction in nasal secretions suggest that nedocromil sodium does play a role inhibiting mast cell degranulation and the subsequent release of PGD₂ and other important mediators.

In addition to inhibiting the early response, nedocromil sodium has been shown to decrease recruitment of cells associated with the late-phase reaction,^{1, 7} to inhibit the release of leukotriene C₄

(an important mediator of nasal congestion), and to have a direct inhibitory effect on airway sensory neurons.²⁵⁻²⁷ Although no single in vitro or in vivo study can predict the therapeutic activity in human beings, these observations suggest the possibility that some or all of these actions may have contributed to the speed of symptom relief and maintenance of therapeutic benefit that nedocromil sodium demonstrated in this study.

Frequently in clinical practice, patients seek medical intervention only after symptoms become noticeable or intolerable. Current topical nasal agents available, although proven to be efficacious, require administration before allergen exposure for optimum control. Nedocromil sodium appears to be not only a drug with a low adverse event profile but one that has the ability to rapidly provide relief in individuals with symptomatic allergic rhinitis.

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