

A multicenter trial of nedocromil sodium, 1% nasal solution, compared with cromolyn sodium and placebo in ragweed seasonal allergic rhinitis

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This study was a double-blind, parallel-group study to evaluate a new medication, nedocromil sodium, 1%, in comparison with placebo and cromolyn sodium, 4%, for treatment of ragweed seasonal allergic rhinitis. Two hundred thirty-three patients (aged 12 to 65 years) from eight centers were randomized to treatment, one spray per nostril, four times daily, with nedocromil sodium, cromolyn sodium, or matched placebo (80, 76, and 77 patients, respectively). All patients had at least a 2-year history of ragweed seasonal allergic rhinitis. Treatment was for 8 weeks during the ragweed season, and daily pollen counts were used to identify the peak 3-week period. Clinic examinations were made before and after the 1-week baseline and after 1, 3, 5, and 8 weeks of treatment. Rhinitis symptoms were recorded each day by the patients. Nedocromil sodium was more effective than placebo ($p < 0.05$) in relieving symptoms as recorded by the patients. Cromolyn sodium was also more effective than placebo, but the difference was not usually significant. Similarly, the active treatments were both better than placebo for clinical parameters measured at visits and for global opinions of treatment, and more rescue therapy was used by the placebo-treated group. There was no significant difference between the two active treatments, but the trend throughout was in favor of nedocromil sodium. Our findings demonstrated nedocromil sodium to be at least as effective as an established therapy (cromolyn sodium) in reducing symptoms of rhinitis during the peak ragweed pollen season. (J ALLERGY CLIN IMMUNOL 1990;86:554-61.)

Allergic rhinitis is a complex disease triggered by the IgE-dependent release of mediators from superficial mast cells and basophils in the nasal mucosa after inhalation of airborne allergens. Release of the preformed intracellular histamine stores and newly formed mediators, such as PGD₂ and leukotriene C₄, results in an immediate hypersensitivity reaction, characterized by rhinorrhea, sneezing, itching, and

Abbreviations used

SAR: Seasonal allergic rhinitis
PGD₂: Prostaglandin D₂

edema, often to be followed after several hours by a late-phase of nasal congestion.¹

Both basophils and nasal mast cells are known to increase in number during the ragweed-pollen season in patients with SAR caused by ragweed.² Recent evidence comparing histamine levels with tryptase levels in nasal washings of patients with rhinitis after pollen challenge suggests that mast cell activation is the major causative factor involved in the immediate nasal-allergic response, since tryptase derives from the mast cells.³ This finding might explain the effectiveness of the mast cell-stabilizer, cromolyn sodium, in SAR,^{1, 4-6} since this compound has been demonstrated to be most beneficial in patients with high preseasonal levels of IgE ragweed antibody,⁷ although

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it does not appear to inhibit basophil histamine release.⁸

Studies by Otsuka et al.⁹ have demonstrated that two types of mast cells occur in nasal scrapings from patients with allergic rhinitis and that the major type present has mucosal mast cell characteristics. Nedocromil sodium is known to be more effective than cromolyn sodium in stabilizing mucosal mast cells derived from monkey airways.¹⁰ Furthermore, a 1% solution administered intranasally 20 minutes before allergen challenge was found effective in preventing symptoms of rhinitis after allergen provocation in patients with allergic rhinitis,¹¹ and recent double-blind, placebo-controlled therapeutic trials have demonstrated nedocromil sodium, 1% nasal spray, to be an effective treatment for SAR caused by birch,¹² grass,¹³ and ragweed pollen.^{14, 15}

Our study is the results of a double-blind, three-way comparative study of nedocromil sodium, 1%, cromolyn sodium, 4%, and placebo nasal sprays used four times daily by ragweed-allergic patients with rhinitis during a period of 8 weeks during the ragweed season.

MATERIAL AND METHODS

Study design

In this double-blind, group-comparative study, patients with ragweed SAR from eight centers were randomized to treatment with nedocromil sodium (Tilarin*), cromolyn sodium (Nasal crom*), or placebo, one spray per nostril, four times daily for 8 weeks. Treatment randomization was preceded by a baseline period of 1 week, which was planned for the start of the ragweed-pollen season in August 1987. The trial-treatment period then spanned the entire ragweed season. Daily pollen counts (Rotorod, Ted Brown Associates, Los Altos, Calif.), carried out at a central laboratory for uniformity, were used to identify the 3-week peak pollen-challenge period for each center.

Patient eligibility for the study was assessed at an initial screening visit before the pollen season and was based on medical history, physical examination, and ragweed skin tests. Laboratory analysis of blood (chemistry and hematology) and urine was carried out to exclude other disorders. All patients entering the study, which was approved by each institutional review board, gave their informed consent in writing. Patients were then supplied with diary cards on which to record severity of rhinitis symptoms, use of concomitant medication, and hours spent in air-conditioned surroundings.

The second clinic visit was timed to coincide with the start of the ragweed season and marked the commencement of the 1-week baseline period. Five additional visits were made: at the end of the baseline, when test treatment was assigned by a computer-generated randomization code, and after 1, 3, 5, and 8 weeks of treatment. At each visit, diary-

TABLE I. Admission characteristics of patients included in the efficacy analysis

Variable	Treatment		
	Nedocromil sodium	Cromolyn sodium	Placebo
Age (yr)			
Mean	30.8	31.5	32.7
Range	12-56	12-66	12-65
Sex			
M	37 (47%)	33 (44%)	34 (45%)
F	41 (53%)	42 (56%)	41 (55%)
Rhinitis history (yr)			
Mean	16.7	17.2	17.7
Range	3-42	3-50	3-40
Immunotherapy	32%	31%	32%

card data were checked and rhinitis symptoms were assessed by the clinician, who also assessed the overall effectiveness of the study drug and recorded any unusual symptoms or adverse experiences that had occurred since the last visit. Patient compliance with test treatment was monitored by weighing the medication bottles at each visit. Blood and urine samples for laboratory analysis were obtained at the final visit, all samples being processed at the same central laboratory.

Patients

From 249 patients screened (30 to 33 at each center), a total of 233 patients were eligible to enter the study and were subsequently randomized to treatment: 80, to nedocromil sodium; 76, to cromolyn sodium; and 77, to placebo. The characteristics of the three treatment groups were comparable (The admission characteristics of patients who were subsequently included in the efficacy analysis are presented in Table I.).

The criteria for eligibility admitted both male and female patients, aged from 12 to 65 years, who had a history of SAR requiring continuous treatment during at least the previous two ragweed seasons and who currently had a positive skin prick test (2+ or more) to ragweed extract. Patients were not admitted if they had any clinically significant abnormal laboratory values or any abnormalities (except for asthma) on physical examination. Women of childbearing potential who were not using contraception were also excluded, as were any patients with rhinitis resulting from additional causes other than pollinosis.

Medications

The test treatments (nedocromil sodium, 1%, cromolyn sodium, 4%, and placebo) were presented in similar metered-dose packs containing 26 ml of aqueous solution with 0.01% edetate disodium and 0.01% benzalkonium chloride as preservative. The treatments were color matched (yellow) by addition of 0.0005% riboflavin to the cromolyn sodium and placebo formulations.

The only other rhinitis medication permitted during the

*Registered trade name of Fisons plc., Pharmaceutical Division, Loughborough, England.

TABLE II. Summary of diary-card efficacy data

Variable	Mean scores						<i>p</i> Values		
	Nedocromil sodium		Cromolyn sodium		Placebo				
	B/L	Peak	B/L	Peak	B/L	Peak	N × P	C × P	N × C
Summary score	4.75	4.65	4.33	4.39	4.96	5.89	0.02	0.14	0.72
Itchy nose	1.10	1.04	0.90	0.92	1.08	1.23	0.15	0.19	0.94
Stuffy nose	1.32	1.28	1.24	1.26	1.34	1.68	0.02	0.05	0.69
Runny nose	1.04	1.11	1.01	1.11	1.10	1.48	0.02	0.20	0.47
Sneezing	1.30	1.21	1.18	1.11	1.39	1.58	0.03	0.09	0.80
Overall symptoms	1.41	1.39	1.50	1.41	1.52	1.78	0.04	0.07	0.95
Sleep disturbance	0.56	0.54	0.53	0.56	0.64	0.74	0.12	0.17	0.90
Pseudoephedrine	0.50	0.47	0.66	0.48	0.66	0.59	0.27	0.13	0.44
Artificial tears	0.38	0.46	0.36	0.54	0.36	0.50	0.71	0.72	0.43

B/L, Baseline; N, nedocromil sodium; C, cromolyn sodium; P, placebo.
Nonparametric analysis.

study was a decongestant, pseudoephedrine tablets, supplied by the investigator on an as needed basis for control of intolerable symptoms. Sinus medications, antihistamines, and cromolyn sodium (other than blinded drug) were disallowed during the study, and oral, ocular, or intranasal steroids were not to be used from at least 2 weeks before the study began. Any patient requiring any of these corticosteroids during the study was regarded as a treatment failure.

Patients receiving regular immunotherapy who were known to develop seasonal rhinitis symptoms were allowed to continue at a constant dose throughout the study. Patients with asthma (27, 23, and 27 receiving nedocromil sodium, cromolyn sodium, and placebo intranasal test treatments, respectively) were allowed inhaled β_2 -agonists and inhaled steroid therapy, but no inhaled cromolyn sodium, oral β_2 -drugs, or theophylline. No ocular medications were permitted except for as needed artificial tears, as prescribed by the investigator.

Efficacy data

Diary-card symptoms (nasal congestion and itching, rhinorrhea, and sneezing), together with overall nasal symptoms, were scored daily by the patients on a 0 to 4 scale of severity (0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe). The sum of the four individual scores, the symptom-summary score, was designated the major primary variable for efficacy.

Sleep disturbance caused by nasal symptoms was also recorded each morning by the patients (0, none; 1, awakened once; and 2, awakened several times).

Clinician assessments of mucosal edema and injection, nasal discharge, and overall severity of rhinitis (0 to 4 scales from none to very severe), together with an effectiveness rating for the study drug (100%, 75%, 50%, 25%, or 0% control of symptoms), recorded at each visit, were designated as secondary variables.

The time period of analysis for primary diary variables was specified as the 3-week peak pollen period; the main

time point for secondary variables was the visit nearest to the peak of the local ragweed-pollen season.

Statistical analysis

A total of 228 patients (78 receiving nedocromil sodium, 75 receiving cromolyn sodium, and 75 patients receiving placebo, Table I) were included in the efficacy analysis, and all those patients randomized (233) were included in the safety analysis. Pretrial comparability of treatment groups, both within and across clinics, was established with Fisher's Exact Test and the Mantel-Haenszel test for binary variables (previous medication, sex, etc.), a two-sample Student's *t* test and two-way analysis of variance for quantitative variables (age, duration of rhinitis, and baseline diary scores), and Wilcoxon rank-sum tests and an extended Mantel-Haenszel analysis for baseline clinic assessments.¹⁶

The primary method used for the direct comparison of differences between the trial treatments was a nonparametric, stratified, randomization covariance analysis, with treatment group mean standardized ranks for the variate (response in peak pollen period) and covariate (baseline).¹⁷

A parametric two-way analysis of covariance (center × treatment) was additionally used to analyze diary-card data, with the baseline score as the covariate and the peak pollen period score as the response. None of the tests for treatment × center interaction approached statistical significance for any treatment group pair, and the main effects model was therefore considered appropriate for the analyses of the combined data across study centers.

Clinic assessments and global opinions were regarded as secondary efficacy variables, with the unit of analysis defined as pooled data from the visit nearest to the peak of the pollen season for each center. (This was visit 5 for one center and visit 4 for the other centers.) Secondary efficacy analysis was by stratified nonparametric analysis of covariance of ranks with change from baseline score as the dependent variable and baseline score as the covariate.¹⁷ Opinions of treatment effectiveness were analyzed with an

TABLE III. Clinic assessments of rhinitis: Changes from baseline scores during peak pollen exposure

	Nedocromil sodium	Cromolyn sodium	Placebo	<i>p</i> Values		
				N × P	C × P	N × C
Mucosal edema						
B/L	1.43	1.48	1.46	0.76	0.86	0.61
Peak	1.2	1.4	1.7	0.01	0.13	0.38
Mucosal injection						
B/L	1.14	1.24	1.2	0.96	0.96	0.46
Peak	0.9	1.0	1.3	0.02	0.01	0.58
Nasal discharge						
B/L	1.18	1.12	1.17	0.78	0.58	0.60
Peak	1.0	1.0	1.3	0.12	0.10	0.85
Overall rhinitis						
B/L	1.32	1.33	1.4	0.82	0.80	1.00
Peak	1.2	1.3	1.5	0.03	0.08	0.37

B/L, Baseline; N, nedocromil sodium; C, cromolyn sodium; P, placebo.
Nonparametric analysis.

extended Mantel-Haenszel-Cochran procedure with standardized rank scores.¹⁶

Two-sided tests with a significance level of $p \leq 0.05$ were used throughout the efficacy analysis. Data from patients who withdrew from the studies for reasons other than treatment failure were included in the analysis up to the point of withdrawal as long as they recorded scores for at least half the peak pollen period. Treatment-failure withdrawals were subsequently assigned the maximum severity score for diary symptoms, and +1 over the worst score possible was assigned for clinic assessments.

RESULTS

Withdrawals

Two hundred thirty-three patients were randomized and began treatment. Twelve subjects withdrew during the treatment period. Two of the withdrawals were due to protocol violations that were, respectively, non-compliance, after 13 days receiving placebo, and pregnancy, after 19 days receiving nedocromil sodium. The other 10 withdrawals included one nedocromil sodium-treated patient, lost to follow-up after 2 days of treatment, and two cromolyn sodium-treated patients. Of these latter two patients, one had increased symptoms after 7 days and the other patient had intercurrent illness (chest symptoms requiring disallowed medication) after 22 days. Seven placebo-treated patients withdrew, including two patients with increased rhinitis symptoms after 4 and 5 days, respectively, and one patient whose increased allergy symptoms required prednisone after 17 days of treatment. Other reasons for withdrawals during placebo treatment were tonsillitis, nosebleeds, and failure to attend visits. Five of the patient withdrawals (two receiving cromolyn sodium and three receiving pla-

cebo) were classed as treatment failures, either because patients withdrew because of lack of treatment effect (one receiving cromolyn sodium and two receiving placebo) or because prednisone therapy was needed to treat a severe exacerbation of allergic symptoms.

Efficacy

Diary-card data. The peak pollen period ran from Aug. 21, 1987, to Sept. 10, 1987 (starting around the same time as trial treatment) in most of the centers. At the Oklahoma center, the ragweed season was expected to be later; trial treatment at this center started August 27, 1987, and peak pollen counts were recorded Sept. 7 to 27, 1987.

Changes in patient diary-card rhinitis-severity scores from baseline to peak pollen exposure in the three treatment groups are compared in Table II. Efficacy is demonstrated where active treatment resulted in lower severity scores than with placebo treatment without increased use of rescue medication.

The diary-card records revealed clear evidence of the efficacy of nedocromil sodium compared with placebo. The symptom-summary score was significantly ($p = 0.02$) less with nedocromil sodium treatment, and this finding was supported by significant differences in favor of nedocromil sodium treatment for nasal blockage and rhinorrhea ($p = 0.02$), sneezing ($p = 0.03$), and overall nasal symptoms ($p = 0.04$). This treatment therefore provided significant protection for all symptoms of rhinitis except itching ($p = 0.15$), which did, however, demonstrate a trend in favor of nedocromil sodium treatment for baseline-adjusted mean scores in seven of the eight centers.

TABLE IV. Global opinions of effectiveness of treatment

% Protected	Clinician			Patient		
	Nedocromil sodium	Cromolyn sodium	Placebo	Nedocromil sodium	Cromolyn sodium	Placebo
100 fully	13	11	6	9	10	5
75 mostly	27	24	16	31	24	20
50 fairly	22	20	22	18	21	21
25 poorly	11	12	18	10	12	16
0 none	4	6	11	9	6	11
Treatment failures	0	2	2	0	2	2
<i>p</i> Values						
N × P		0.001			0.03	
C × P		0.03			0.09	
N × C		0.27			0.66	

N, Nedocromil sodium; C, cromolyn sodium; P, placebo.

Extended Mantel-Haenszel-Cochran test.

The supplemental parametric analysis was in agreement, indicating a strongly significant efficacy difference in favor of nedocromil sodium over placebo treatment ($p = 0.008$ and 95% confidence interval, 0.31 to 1.95, for the symptom-summary score). This effect was consistent across the centers ($p = 0.50$ for center × treatment interaction).

For cromolyn sodium, nonparametric analysis of the primary variable, the symptom-summary score, did not demonstrate a significant improvement, although the severity-score increase from baseline to peak pollen was only 0.06 compared with 0.93 for placebo. Stuffy nose was the only individual symptom to demonstrate a significant ($p = 0.05$) improvement in the cromolyn sodium-treated group, but strong trends were noted for other symptoms. Additionally, some of the advantages over placebo treatment reached significance in the supplemental parametric analyses, including the summary score ($p = 0.02$) and overall nasal symptoms ($p = 0.01$). Trends favored cromolyn sodium over placebo treatment for all variables in most centers.

There were no statistically significant differences between the nedocromil sodium-treated group and the cromolyn sodium, active-treatment control group, although baseline-adjusted treatment differences demonstrated trends (in favor of nedocromil sodium) at three or more of the study centers for each variable. Sleep disturbance caused by rhinitis symptoms increased slightly in placebo-treated patients but was unaltered from baseline in the active-treatment groups. The differences were not significant, but trends favored active treatment over placebo treatment with nedocromil sodium treatment favored over cromolyn sodium treatment at four of the centers.

Active-treatment groups tended to use less rescue medication, but differences between the groups were not significant. Treatment groups were comparable for time spent in an air-conditioned environment during both baseline and peak pollen periods. Hours spent in air conditioning was not therefore a factor influencing symptom severity in the three groups.

Clinical assessments

When clinicians' assessments of signs of rhinitis at the peak pollen visit were compared with baseline assessments (Table III), the direction of treatment-group differences favored nedocromil sodium over placebo in each center, and over all centers, there was a significant difference in favor of nedocromil sodium for mucosal edema ($p = 0.01$) and injection ($p = 0.02$) and for overall rhinitis severity ($p = 0.03$). Nasal discharge was reduced in comparison to placebo treatment in six of the centers, and the overall trend was in favor of nedocromil sodium treatment, although this trend was not significant ($p = 0.12$). The cromolyn sodium-treated group also demonstrated improvements over placebo treatment for each variable, with a significant ($p = 0.01$) difference for mucosal injection. There were no significant differences between the two active treatments.

For the clinicians' opinions (Table IV), the overall difference favoring nedocromil sodium over placebo was statistically significant ($p = 0.001$), and the patients also favored nedocromil sodium over placebo ($p = 0.03$). Treatment was judged by the clinicians as at least fairly effective for 81% of patients receiving nedocromil sodium compared with 59% receiving placebo. Corresponding patients' opinions were 75% versus 61%. The overall difference favoring cromolyn sodium over placebo was significant ($p = 0.03$) for

TABLE V. Adverse event reports: Frequency of total (≥ 10) and treatment-related events

Event	Nedocromil sodium	Cromolyn sodium	Placebo
Headache			
Total	43 (54%)	30 (39%)	23 (30%)
Treatment-related	5 (6%)	2 (3%)	2 (3%)
Sneezing			
Total	7 (9%)	4 (5%)	8 (10%)
Treatment-related	4 (5%)	2 (3%)	7 (9%)
Taste			
Total	11 (14%)	3 (4%)	2 (3%)
Treatment-related	10 (13%)	2 (3%)	2 (3%)
Pharyngitis			
Total	5 (6%)	4 (5%)	6 (8%)
Treatment-related	1 (1%)	0 (0%)	0 (0%)
Nose Burning			
Total	2 (3%)	8 (11%)	1 (1%)
Treatment-related	2 (3%)	8 (11%)	1 (1%)
Conjunctivitis			
Total	3 (4%)	1 (1%)	6 (8%)
Treatment-related	0 (0%)	0 (0%)	0 (0%)

the clinicians' opinions, whereas patients' opinions demonstrated a similar trend ($p = 0.09$). Seventy-three percent (both patients and clinicians) judged cromolyn sodium to be at least fairly effective. There was no significant difference between active treatments.

Safety

No serious adverse events occurred during the trial. Fifty-one (64%) of the 80 patients in the nedocromil sodium-treated group, 41 (54%) of the 76 patients receiving cromolyn sodium, and 46 (60%) of the 77 placebo-treated patients reported at least one unusual symptom during the double-blind period. Headache was the most common event, reported by 54% of the nedocromil sodium-treated group, 39% of the cromolyn sodium-treated group, and 30% of the placebo-treated group. Adverse events most commonly judged by the clinician to be related to study medications were bad taste (13%, 3%, and 3% of patients from the nedocromil sodium-, cromolyn sodium-, and placebo-treated groups, respectively), sneezing (5%, 3%, and 9%, respectively), and nasal burning (3%, 11%, and 1%, respectively). Details are presented in Table V. No untoward trends were observed in any treatment group with regard to blood chemistry, hematology, or urinalysis.

DISCUSSION

The objective of this study was evaluation of the efficacy and safety of a 1% nasal formulation of nedocromil sodium when it is used four times daily in ragweed SAR. Eight centers were involved to provide

a large enough study population, and local pollen counts were used to ensure that efficacy data analyses coincided with maximum pollen challenge in each center. The group-comparative design of the study was strengthened by inclusion of a positive control, cromolyn sodium, in addition to the negative placebo control, eliciting a more realistic measure of the potential therapeutic value of the trial drug.

Cromolyn sodium, 4%, was selected as positive control for two reasons: first, its established efficacy as a preventive treatment for rhinitis,⁶ and second, because of its mechanism of action, based, at least in part, on the ability of cromolyn sodium to stabilize the membranes of mast cells and prevent release of their proinflammatory mediators. There is considerable evidence to implicate nasal mast cells in the pathophysiology of SAR, including a seasonal increase in numbers of these cells that occurs during pollen exposure and which coincides with a growing severity of rhinitis symptoms as the season progresses. Basophils, as well as mast cells, increase in number during pollen challenge in patients with SAR,¹⁸ but a recent challenge study,³ in which mast cell-specific tryptase levels were measured in the nasal washings, demonstrated that mast cell activation is the major factor involved in the immediate nasal-allergic response. Both mucosal and connective tissue subtypes of (human) mast cells are known to contain tryptase, whereas chymase occurs only in connective tissue mast cells.¹⁹

Intranasal ragweed-antigen challenge has been used to correlate the immediate clinical response of patients with SAR with the appearance in nasal washings of

mast cell-derived histamine and PGD₂.²⁰ In subjects whose immediate response to antigen provocation was followed by a recurrence of symptoms 3 to 11 hours after challenge, the late increase in nasal histamine was not accompanied by a rise in PGD₂ levels, suggesting that the mediators of late antigen-induced rhinitis are derived from basophils rather than from mast cells.²¹

Although it is generally accepted that cromolyn sodium does not inhibit basophil degranulation,⁸ a recent study has suggested the possibility that both nedocromil sodium and cromolyn sodium could have an indirect inhibitory effect on basophils that are involved along with eosinophils in an inflammatory reaction. Beauvais et al.²² found that, although neither of these compounds directly inhibited human basophil degranulation, they did inhibit IgG4-dependent basophil degranulation in the presence of eosinophils, which activity was demonstrated to derive from inhibition of the IgG4-induced release of cationic proteins from the eosinophils. This *in vitro* evidence is supported by earlier histopathologic observations in nasal biopsy specimens from sufferers from hay fever that suggested that cromolyn sodium did have inhibitory effects, *in vivo*, on basophils that were actively involved in the disease process.²³

Nasal eosinophils and basophils,^{2, 24, 25} as well as mucosal mast cells,⁹ demonstrate a characteristic increase in patients with SAR during the pollen season, together with a local increase in inflammatory mediators that parallels symptom severity.²⁶ With continued pollen exposure, this chronic allergic reaction leads to a state of hypersensitivity of the nasal mucosa to histamine and irritants of any sort, accompanied by a pronounced hyperreactivity of the nasal glands to parasympathetic stimulation.^{27, 28} This nasal "priming" effect, described by Connell²⁹ in 1969, results in an exacerbation of rhinitis symptoms, which may then continue for some time after the peak of the pollen season has passed. The ideal treatment for SAR would need to abolish the entire inflammatory sequence from its inception in an IgE-loaded mast cell on inhalation of the season's first pollen grain. In practice, a combination of preventive and rescue medications must often be used to control the disease.

The advantages and disadvantages of the therapeutic options available to physicians who treat patients with allergic rhinitis have recently been reviewed by Busse³⁰ in the light of increased understanding of the mechanisms by which the various treatments are able to reduce the symptoms of rhinitis. For nasal cromolyn sodium, nearly two decades of use have established an impressive safety record and have proved the therapy to be effective for many patients with allergic rhinitis. However, the response to cromolyn sodium

can vary in an unpredictable manner, which, Busse³⁰ suggests, may be related to the presence of mast cell subsets possessing differential sensitivity to the drug. Demonstration of the insensitivity to cromolyn sodium of mucosal-type mast cells in the airways of subhuman primates¹⁰ appears to support this hypothesis, which might also be applied to the interpretation of our results here in comparing cromolyn sodium therapy with nedocromil sodium therapy. Both drugs were effective. There were no statistically significant differences between the drugs, although some trends were noted in favor of nedocromil sodium. Comparison of the two drugs with placebo, in contrast, elicited an indication of stronger absolute efficacy with nedocromil sodium, perhaps reflecting the ability of this compound, unlike cromolyn sodium, to stabilize more than one subset of mast cells in the nasal mucosa. The final answer to these questions must await more detailed investigations.

The conclusion from our present study is that nedocromil sodium, 1% nasal solution, used four times daily through the pollen season, provides safe and effective therapy for ragweed SAR. This new formulation was at least as effective as an established topical medication, cromolyn sodium, for relief of rhinitis symptoms during peak pollen exposure.

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