

In summary, the above results support the importance of American cockroach whole body allergens as significant sensitizing agents in the induction/exacerbation of allergic respiratory disease. Our findings also suggest the presence of "major" allergens in "fraction 2" of AWBE and support the presence of both species-specific and shared, interspecies allergens between AWBE and GWBE.

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Intranasal nedocromil sodium in the treatment of ragweed-allergic rhinitis

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*Nedocromil sodium (NS), a new pyranoquinoline dicarboxylic acid derivative, reported to be effective against both mucosal and connective tissue-type mast cells, was studied in ragweed-allergic rhinitis (RAR). Thirty-six patients with RAR were studied in an 8-week, double-blind, placebo-controlled trial. Stratification was based on prick skin test sensitivity and severity of signs and symptoms of previous RAR. NS (1% solution) in a dose of 0.13 ml of nasal spray was administered to each nostril, a minimum twice daily. Concomitant medications were limited to ingested terfenadine, ocular cromolyn, and inhaled medications. Symptoms and medications were noted daily. Active-treatment and placebo-treatment groups were comparable. There were less symptoms of runny nose and itchy eyes in the active-treatment group ($p < 0.05$) and also less antihistamine, $p < 0.004$. Patients in the active-treatment group were more likely to conclude that symptoms were improved by the nasal spray ($p < 0.01$). No side effects were reported. This study indicates that NS is effective and well tolerated in RAR. (*J ALLERGY CLIN IMMUNOL* 1988;81:570-4.)*

NS is a new pyranoquinoline dicarboxylic acid derivative that is reported to be effective against both mucosal and connective tissue-type mast cells.¹ In

Abbreviations used

NS: Nedocromil sodium
RAR: Ragweed-allergic rhinitis

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contrast, cromolyn sodium appears to be effective only against connective tissue-type mast cells.² NS has been demonstrated to be effective in treatment of asthma³ and inhibiting the airway responses to exer-

TABLE I. Patient characteristics

Variable	NS	Placebo
No.	18	18
Age (yr)		
Mean	43.4	41.0
Range	24.2-57.0	27.7-56.9
Sex		
M	5	10
F	13	8
Age at onset of rhinitis (yr)		
Mean	20.8	19.3
Range	5-45	6-40
Previous hyposensitization		
Yes	14	18
No	4	0
Previous therapies for rhinitis		
Antihistamines	17	16
Eyedrops	2	5
Nasal decongestant	0	1
Nasal sprays	14	17
Other allergies		
Yes	10	9
No	7	9
Not reported	1	0
Time spent outside week days (hr)		
Mean	2.9	5.4
Range	1-8	0.5-16
Weekend (hr)		
Mean	5.5	8.5
Range	1-10	2-16
Skin test titration end point		
7	2	1
6	0	2
5	5	3
4	8	8
3	3	4
Mean	4.4	4.3

cise,^{4,5} and the immediate and late airway responses to antigen challenge.^{6,7}

In patients with RAR, during ragweed season, the mast cells in the nasal epithelium are numerous and increase in number, and most of these cells have features of mucosal mast cells.⁸ It was, therefore, of interest to test the therapeutic efficacy of topical NS in ragweed-allergic subjects during seasonal exposure to ragweed.

MATERIAL AND METHODS

Thirty-six patients were selected from the Chest/Allergy Clinics of St. Joseph's Hospital and McMaster University

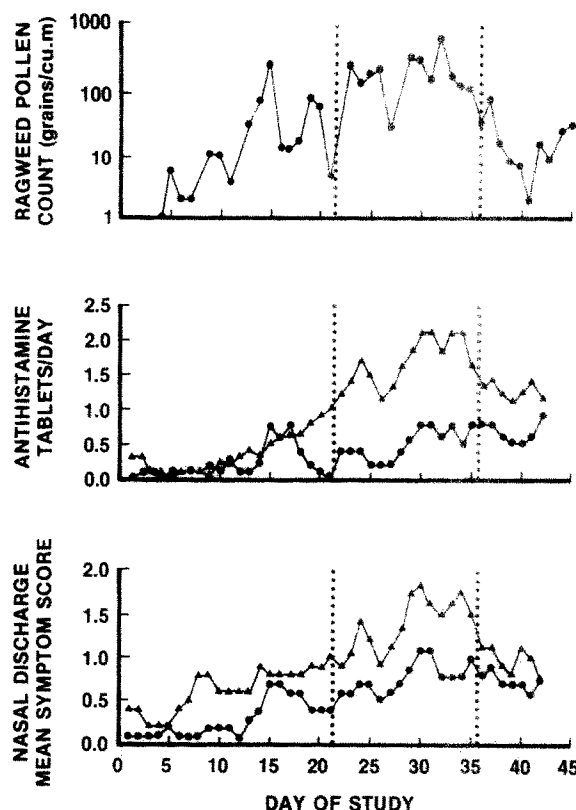


FIG. 1. Ragweed pollen count, supplemented antihistamine use, and nasal discharge symptom score during the course of the study. Day 1 corresponds to August 5. In middle and lower panels, NS-treated group (●●●) and placebo-treated group (▲▲▲). The time period between the two vertical dotted lines was used for statistical analysis. There is less antihistamine use and less nasal discharge in the NS-treated group.

Medical Center in Hamilton. All had a history of at least 2 years of moderate to severe rhinitis and conjunctivitis in August and September, typical of ragweed-pollen allergy. All had positive skin prick tests with ragweed-pollen extract (Pharmacia [Canada] Inc., Dorval, Canada). Excluded from the trial were women who were pregnant, lactating, or at risk of becoming pregnant. Also excluded were patients who had diseases of the nose not associated with RAR, patients receiving drugs, such as corticosteroid or cromolyn (nasal) that can affect the nasal mucosa, or patients who had been treated with hyposensitization therapy in the preceding 12 months or who had any major diseases likely to cause abnormal results in the laboratory tests performed. Ethical approval for the study was granted by McMaster University Medical Center Research Advisory Group, and signed informed consent was obtained from each patient.

Stratification of patients for randomization was performed initially based on the results of skin prick test end point titration (smallest concentration producing a wheal compared to buffer as a negative control) in prick tests with seven serial tenfold dilutions of ragweed-pollen extract

TABLE II. Severity of symptoms (mean values)

Symptom	NS (n = 18)	Placebo (n = 15)	Probability
Sneezing			
Night	0.61	0.62	0.84
Day	0.90	1.31	0.12
Nose			
Stuffy			
Night	0.67	1.13	0.07
Day	0.79	1.42	0.052
Running			
Night	0.53	0.71	0.40
Day	0.81	1.37	0.04*
Eyes itching or watering			
Night	0.32	0.64	0.22
Day	0.54	1.05	0.03*
Cough			
Night	0.05	0.13	0.13
Day	0.06	0.15	0.16

Severity scale: 0 (none) to 3 (severe).

*Significance, $p < 0.05$.

(Pharmacia [Canada] Inc.) starting at 100,000 allergy units per milliliter. Subjects with equal skin test reactivity were secondarily stratified on the basis of a symptom score obtained from the history of symptoms in the previous ragweed season. From the stratification procedure, patients were assigned on a double-blind basis to the treatment regimen in blocks of four patients. Within each block, two patients received placebo and two received NS. Each NS dose was 0.13 ml of 1% solution administered intranasally. The optimal dose of NS for treatment of allergic rhinitis is not known; consequently, the subjects were allowed to increase from the initial dose four times a day to two doses four times a day if symptoms were not well controlled initially. The placebo solution was riboflavin, which matches the color of the medication. Concomitant medication for rhinitis taken during the study was restricted to short-acting selective antihistamine (terfenadine), if symptoms were not controlled by the experimental treatment, and topical cromolyn for eye symptoms or inhaled salbutamol for chest symptoms. If chest symptoms were not controlled, inhaled cromolyn or beclomethasone could be added. Patients were encouraged to use sufficient antihistamine to keep hay fever symptoms under control. Significantly less antihistamine use by the active-treated group would be one outcome indicating efficacy. Diary cards were kept by patients who were asked to record the severity (on the scale of 0, absent, to 3, severe) and frequency (0, absent; A, occasional episodes; B, many episodes; or C, continuous) of sneezing, nasal obstruction, rhinorrhea, eye itching or watering, and cough. Night and day symptoms were recorded separately.⁹ The use of the test solution, antihistamine, salbutamol, cromolyn sodium (Opticrom; Fisons Corp., Bedford, Mass.), or other medications were also recorded daily. The study was designed

to cover a period of approximately 8 weeks per patient. There was a short baseline period in which symptoms and medications were recorded and followed, beginning on August 9, by the 6-week treatment period.

Each patient made four visits to the clinic. At the first visit, the suitability for inclusion was evaluated. On the second visit, laboratory test results were checked, medications were assigned, and patients were instructed on how to take the medications. At the third visit, 1 week after starting the medication, the procedure was reviewed, and diary cards were checked. At the final visit, diary cards were collected, and samples were taken for laboratory tests. At each visit, a nasal physical examination was performed to assess the edema of the turbinates, redness of the mucosa, and the amount of mucous in each nostril on a scale 0, none, to 4, very severe. Assessment was also made by the patient of the symptoms experienced since the previous visit, using the same scale as the diary card. At the final visit, the patient and the clinician recorded opinions on the efficacy of the test solution in treatment of the rhinitis.

Daily ragweed-pollen counts in grains per cubic meter for a 24-hour period were performed with a Hirst volumetric spore trap (Burkard Manufacturing Co., Ltd., Rickmansworth, Hertfordshire, England), located on the roof of the Regional Laboratory in Hamilton, Ontario, at a height of 20 feet above the ground, and achieved a level that was sufficient to cause symptoms in the study group. The period between August 27 and September 10 was identified as the peak pollen time and was used in the analysis of the trial. In all statistical comparisons, two-tail tests have been used, and the probability (p) of $<5\%$ indicates significance (Mann-Whitney U for nonparametric tests and Student's t test for parametric analysis).

RESULTS

There were 36 patients in the trial. An equal number was assigned to the placebo- and NS-treatment groups. Characteristics of subjects in the groups are compared in Table I. Five men and 13 women with a mean age of 43 (24 to 57) years received NS treatment. In the placebo-treatment group of 10 men and eight women, the mean age was 41 (27 to 57) years. Half the placebo-treatment group and just more than half the NS-treatment group suffered from other allergies. Subjects in the two groups spent similar amounts of time out of doors. The level of allergy, assessed by skin test titration, was similar in the two groups, as might be expected insofar as this was the criterion for the initial stratification procedure. The severity of symptoms of rhinitis was also the same in the NS-treatment and placebo-treatment groups. Few symptoms were present at the start of the study, and symptoms that were present were mild to moderate.

Two patients in the NS-treatment group and seven patients in the placebo-treatment group increased their medication more than one dose each nostril four times a day for four days or more during the study period. Four patients were withdrawn from the study, one from the NS-treatment group and three from the placebo-treatment group. Three patients (one, active-treated; two placebo-treated) withdrew after 18, 21, and 28 days, respectively, because of uncontrolled symptoms. The symptoms of these patients were included in the analysis until additional treatment was needed. One patient (receiving placebo) failed to return on the last visit and did not bring in the diary cards. The mean daily severity scores for each symptom during the peak pollen period is presented in Table II. There are generally less symptoms in the NS-treatment group. A statistically significant difference in favor of NS was present in the daytime scores of the nasal discharge ($p = 0.04$) and eye itching and watering ($p = 0.03$). Scores for daytime stuffy nose favored NS, but the difference was not significant ($p < 0.1$). Fourteen patients in the placebo-treatment group and eight patients in the NS-treatment group took antihistamine. The total amount used was significantly less ($p = 0.004$) in the NS-treated group (Fig. 1). Eight patients in the NS-treated group and 11 in the placebo-treated group used the eyedrops during the peak pollen period; this difference was not significant.

Only three patients reported unusual symptoms; two, taking NS, and one, taking placebo. Nasal irritation and stinging were experienced with the active-treatment group. The placebo-treated subject reported dryness of the nasal passages. This patient had been

taking the terfenadine regularly. The severity of these symptoms in all three patients was mild.

DISCUSSION

All categories of symptoms were less with NS treatment. The difference was statistically significant in the categories of nasal discharge and eye itch.

The global assessment by the patient and clinician was also significantly in favor of NS. The difference between the two treatment groups that was most significant was in the amount of antihistamines required ($p = 0.004$). Thus, the active-treatment group had fewer symptoms, despite much less use of antihistamine. The lower level of eye symptoms in the active-treated group was unexpected, insofar as the amount of exposure and level of sensitivity of the subjects were judged to be virtually the same in the two treated groups, and the active-treated group used less antihistamine. Moreover, there have not been reduced eye symptoms in trials of beclomethasone dipropionate aerosol treatment of RAR.¹⁰⁻¹² It is possible that the improved status of the nasal symptoms in the active-treated group results in an improved sense of well-being with resulting reduced attention to symptoms, including eye symptoms.

In conclusion, NS is effective in reducing the symptoms of seasonal RAR and in replacement of antihistamine in the treatment. The relative efficacy and proper place in the treatment regimen must await further observations.

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Double-blind comparison of terfenadine, chlorpheniramine, and placebo in the treatment of chronic idiopathic urticaria

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The efficacy of terfenadine, a nonsedating H₁ antihistamine, in the management of chronic idiopathic urticaria was compared with chlorpheniramine and placebo in a parallel multicenter trial. Subjects with symptoms of hives for 3 days per week for at least 6 weeks were initially screened and admitted if no identifiable cause for symptoms could be determined. Patients entered a single-blind placebo period, and if hives of moderate severity were present for at least 3 days during the week, they were randomly assigned in a double-blind fashion to take terfenadine, 60 mg twice daily, chlorpheniramine, 4 mg three times a day, or placebo for 6 weeks. Data were analyzed for 122 patients. Those patients receiving both active treatments noted significant improvement in symptoms: pruritus, redness, number of hives, and waking hours during which hives were present, at the end of the first day of therapy. Symptom control by terfenadine was statistically superior to placebo during all 6 weeks, as rated by both patients and investigators. However, statistical significance was not achieved for chlorpheniramine at all observation points. Diphenhydramine was permitted as a relief medication for refractory symptoms and was taken by 52% of subjects receiving placebo, 26% taking chlorpheniramine, and only 9% of patients who were receiving terfenadine. In addition to providing superior symptom control, terfenadine caused less drowsiness and fatigue than chlorpheniramine. Terfenadine is a useful therapeutic agent for primary management of chronic idiopathic urticaria. (J ALLERGY CLIN IMMUNOL 1988;81:574-9.)

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