

The effect of cromolyn sodium powder as a treatment for ragweed pollinosis

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The effect of treating ragweed pollinosis with intranasal cromolyn sodium powder was evaluated in 26 patients in a double-blind clinical study. Thirteen matched patient pairs were treated by either nasal insufflation of cromolyn sodium powder, 20 mg three times daily, or by a placebo powder. Patients were monitored for severity of symptoms by means of daily symptom diaries collected weekly throughout the pollen season. Serum samples were obtained in July prior to the ragweed season and following the ragweed season during the first and fourth weeks of October for the determination of ragweed-specific IgE antibody levels by the radio-allergosorbent test. A significant reduction in symptom severity was observed in the treated patients with high preseasonal levels of IgE antibody to ragweed. Initially the levels of IgE antibody to ragweed did not differ between the two groups. IgE antibody levels increased in both groups after pollen exposure, but the treated group showed a significantly greater rise in IgE antibody levels. The results suggest that treatment with cromolyn sodium enhanced IgE antibody response to pollen exposure and significantly reduced the severity of hay fever symptoms in patients with high preseasonal levels of IgE antibody to ragweed.

The value of cromolyn sodium as an adjunctive treatment for patients with bronchial asthma has been confirmed in numerous double-blind clinical trials. It is particularly useful as a prophylactic treatment in patients with extrinsic forms of asthma,¹⁻⁸ although it has also been found useful in treating intrinsic asthma.^{9, 10} The exact mechanism of action of cromolyn sodium is unknown, but evidence suggests that it stabilizes the mast cell membrane, thus preventing the release of the mediators of anaphylaxis.¹¹ This has led to the suggestion that nasal administration of cromolyn sodium might be of value in preventing symptoms associated with allergic rhinitis. Recently, cromolyn sodium has been found to have a beneficial effect on the symptoms of perennial allergic rhinitis.^{12, 13} However, several double-blind trials of the effect of cromolyn sodium in allergic rhinitis due to grass and tree pollen have yielded conflicting results.¹⁴⁻¹⁹ In this study we administered cromolyn sodium powder and evaluated its effects on the symptoms of ragweed pollinosis and its effects on the changes in levels of IgE antibodies to ragweed pollen.

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TABLE I. Clinical data on patients with ragweed pollinosis

	Control	Treated
No. of patients	13	13
Age, yr		
Range	14-53	17-66
Mean	33	35
Sex, male/female	8/5	9/4
Duration of hay fever, yr		
Range	8-40	5-47
Mean	21	21.5
Preseasonal RAST (per cent of counts bound)		
Range	1.06-22.83	1.10-18.31
Mean	7.59	7.67

METHODS OF INVESTIGATION

Patients

The double-blind investigation was carried out during the ragweed pollen season in 1973. The study was approved by the Human Studies Committee of the Mayo Foundation and fully informed consent was obtained from each patient. Twenty-six patients participated in the study, 17 males and 9 females, ranging in age from 14 to 66; all had had symptoms of ragweed pollinosis for several years. None of the patients had received immunotherapy during the five years prior to the study. Twelve of the patients had a family history of allergic rhinitis and/or asthma. All of the patients had positive reactions to skin tests with ragweed pollen extract and elevated levels of IgE antibody to ragweed as measured by the radio-allergosorbent test (RAST).²⁰

Each patient was tested intradermally with extracts of short, giant, and western ragweed (100 protein nitrogen units [PNU]/ml) and *Alternaria*, *Hormodendrum*, *Helminthosporium*, and *Aspergillus* (500 PNU/ml) (Center Laboratories, Port Washington, N. Y.). Sufficient allergen was injected to produce an initial wheal 3 mm in diameter. Results were recorded in millimeters of the diameter of the wheal of the maximally reacting ragweed and mold extract at 15 min. Twenty of the 26 patients had resulting wheal diameters of greater than 8 mm with ragweed extract, and all of the patients had reactions with wheal diameters greater than 5 mm to ragweed extract. In addition to the positive skin tests to ragweed pollen, 10 of the 26 patients also had definite positive wheal reactions to mold extract; however, only 2 of these reactions were greater than 8 mm in wheal diameter. The dominant sensitivity in all patients appeared to be to ragweed pollen in that the patients had their onset of symptoms coincident with the appearance of ragweed pollen in August.

The patients were interviewed to estimate the amount of environmental exposure to ragweed pollen during the season, based on occupation, presence of air conditioning at home and work, and planned trips or vacations. The patients were paired according to the following criteria: (1) preseasonal RAST levels, (2) estimated exposure to ragweed pollen during the pollen season, (3) age, and (4) skin test results, i.e., all of the patients with positive skin tests only to ragweed were paired and those who also had positive skin tests to molds were paired to others who had positive skin reactions to the same molds. A list of paired patients was submitted to a third party who was responsible for the packaging and distribution of the medication and placebo capsules.

Each patient was asked to maintain a daily diary summarizing his symptoms and medication, which was collected weekly. The symptom scoring was patterned after that devised by Norman, Rhyne, and Mellits²¹ in which the severity of symptoms (sneezing, coughing, stuffy or runny nose, red, itchy eyes, and asthma) during the 12-hr periods from midnight to noon and noon to midnight each day was scored on the basis of 0 to 3. Each 4-mg unit of chlorpheniramine or equivalent used during the 12-hr period was assigned a score of 1. An average symptom score was determined for each patient over the entire season as well as

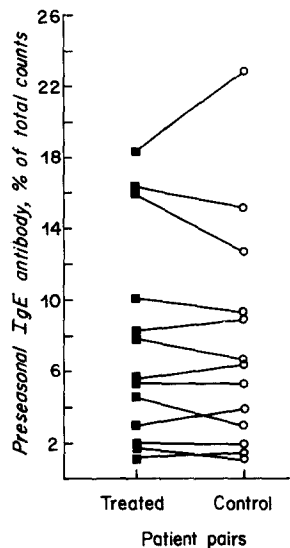


FIG. 1. Preseasonal levels of IgE antibody determined in initial pairing RAST. Lines connect observations on patient pairs. Results recorded as percentage of total counts bound. (Serums from a nonallergic control yielded value of 0.27% in assay.)

over the period of peak pollen exposure. An average symptom score was also determined daily for both the control and the drug-treated groups.

After the scores were tabulated and the code was broken, it was found that the characteristics of the control and treated groups were similar in sex ratio, age, duration of hay fever, and preseasonal RAST values (Table I). The preseasonal RAST values for the paired patients are presented in Fig. 1.

Treatment

The patients in the treatment group were given capsules of cromolyn sodium containing 20 mg of cromolyn sodium and 20 mg of lactose powder (added to improve the flow properties of the material). The patients in the control group were given identical capsules filled with a mixture of 30 mg powdered lactose and 10 mg anhydrous sodium sulfate which has been used as a placebo preparation in experiments involving oral administration of cromolyn powder since it mimics the taste of cromolyn sodium.² Both the placebo and treatment preparations were administered with a turbo-inhaler (Spinhaler, Fisons Corporation, Bedford, Mass.) with a special silicone rubber sleeve adapter permitting nasal usage. The patients were instructed to insufflate the contents of 1 capsule, 3 times daily, dividing the doses between the two nostrils and alternating administration between nostrils. The study began August 6, prior to the ragweed pollen season, and continued throughout the pollen season until September 23. Medications were distributed on a weekly basis. We found that it was necessary to include a desiccant in the packages of the medication because the capsules had a tendency to absorb moisture and resist being pierced in the Spinhaler. Both the treated and control patients were allowed to use antihistamines as needed, keeping a record of each dose. One patient withdrew from the study after two weeks of treatment because of nasal irritation from using the medication. He was later found to have been in the placebo group. His treatment pair was eliminated when symptom results were calculated, but this pair was included in the analyses of the changes in IgE antibodies. Therefore, in estimating relief from symptoms, 12 patient pairs were analyzed, whereas for changes in IgE antibodies, 13 patient pairs were analyzed.

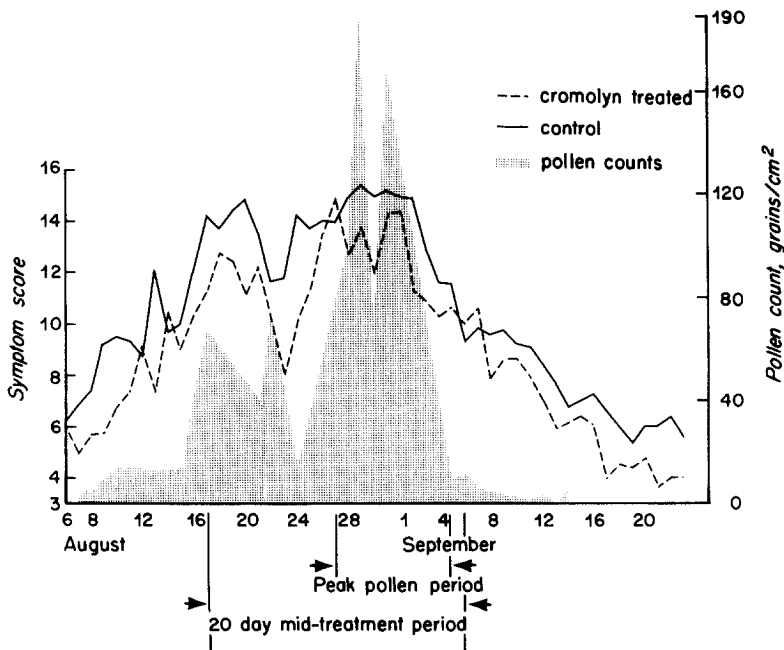


FIG. 2. Comparison of pollen counts and symptom scores for patients with ragweed pollinosis: 12 control patients; 13 cromolyn-treated patients.

Analysis of serum for IgE antibodies

A serum specimen was obtained from each patient at the time of the initial visit when preliminary skin tests were performed in July. Two additional serum samples were obtained during the first and fourth weeks of October. Serum samples were stored at -20°C . IgE antibody to ragweed antigen was measured by the radioallergosorbent test, performed essentially as described by Yunginger and Gleich²² except: (1) the polymer was prepared from short ragweed extract that had been partially purified by two passages through Sephadex G-25; (2) 20 ng of radiolabeled anti-IgE were used in the second stage rather than 2 ng; and (3) 0.2% bovine serum albumin diluent was used in the first stage and 4% fetal calf serum diluent was used in the second stage.²³ The July serums were analyzed in a single assay and the levels of IgE antibody were expressed as the ratio of counts bound divided by total counts added $\times 100$. The results of this assay for the patient pairs are shown in Fig. 1.

Following the completion of the study, all bleedings from the patients were analyzed in a single RAST assay to determine whether the groups differed in the magnitude of the seasonal rises. We have previously shown that in most patients in our area, peak levels of IgE antibody are reached between mid-September and mid-October.²⁴ In the assay to determine rises in IgE antibody, the results were standardized by expressing them in terms of the reactivity of a serum pool from 5 subjects highly sensitive to ragweed pollen. We have shown that there is a linear relationship between the logarithm of the RAST results (counts bound divided by counts added $\times 100$) and the logarithm of the μL of serum pool analyzed.²⁵ Moreover, dose-response curves of serums from patients whose sensitivity to ragweed varied markedly had very similar slopes when plotted in this manner. Therefore, the serum pool, arbitrarily defined as containing 10,000 U/ml, was analyzed as a standard and the reactivity of individual serums was expressed in terms of these units. The correlation coefficient for the regression line for the serum pool, 6 points from 1.2% counts bound to 21.0% counts bound, was +0.99. Serum from nonallergic subjects bound 0.05% of counts added.

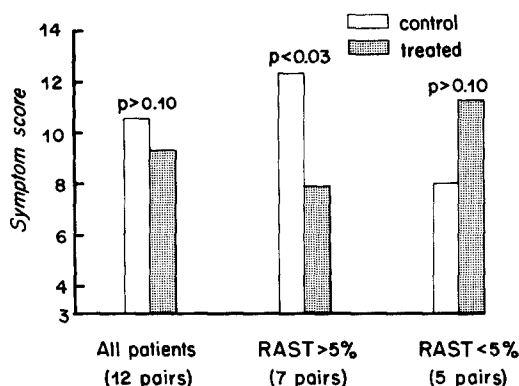


FIG. 3. Average symptom scores of treated and control patients during treatment period.

Statistical analyses

Differences among patient pairs were analyzed by the Wilcoxon signed rank test.²⁶ For testing the effect of drug vs placebo, 1-tailed tests of significance were employed, whereas for analysis of differences in magnitude of rises of IgE antibodies, 2-tailed tests were used.

Pollen counts

These were recorded as ragweed pollen grains per square centimeter (Fig. 2) of a slide exposed for 24 hr in a Durham gravity sampler.²⁷ Pollen counts following August 23 were also made from a roto-slide sampler,²⁸ and these counts in general corroborated the results obtained from the Durham sampler. The data from these counts were used primarily in defining the span of the ragweed pollen season and for determining the peak weeks of exposure to ragweed pollen.

RESULTS

Average symptom scores for the 13 treated and 12 placebo patients who completed the study were computed over three periods of time—the total treatment period, 7 wk; a 20-day midtreatment time span; and a 10-day period of maximum pollen exposure (Fig. 2). Because the ragweed pollen count was quite low in the first and last portions of the trial, we determined whether there were differences in symptoms between the treated and placebo groups for the 20-day midtreatment period and for the 10-day peak pollen period. At this time the effect of the drug, if significant, should have been most evident. Scores of the treated patients tended to be lower than those of the placebo patients (Fig. 3) when all patients were considered over the total treatment period, but the differences were not statistically significant when the patient pairs were compared ($p > 0.10$, signed rank test).

To evaluate further the effect of the drug, patient pairs were divided into two groups based on preseasonal RAST values. As shown in Fig. 3, those 7 patient pairs with preseasonal RAST values above 5.0% binding demonstrated a significant difference in symptom scores ($p < 0.03$, signed rank test) between the placebo and treated groups over the total treatment period. Similar differences were observed over the period of peak pollen exposure ($p < 0.03$, signed rank test) and for the 20-day midtreatment period ($p < 0.05$, signed rank test).

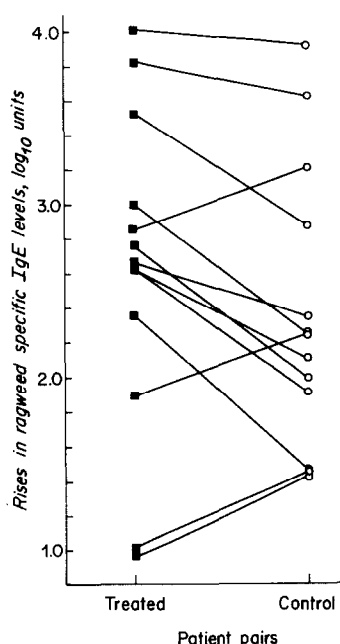


FIG. 4. Maximum rise of IgE antibody determined as difference between peak October RAST level and July RAST level; results recorded as $\log_{10}$ RAST units.

Three patient pairs of the 7 with RAST values above 5.0% binding had asthma, but in all of these the symptoms were mild. The difference in symptom scores between placebo and treated pairs with preseasonal RAST values below 5.0% binding, 5 pairs, was not significant.

To determine if treatment affected the seasonal rises in IgE antibodies, the 3 serum samples obtained from the patients were analyzed in a single RAST assay. The treated group demonstrated a significantly greater rise in ragweed-specific IgE antibodies than did the placebo group ($p < 0.05$, signed rank test). In Fig. 4, differences in the IgE antibody rise for the paired patients are shown. In 9 of the 13 patient pairs the treated member demonstrated a greater rise in IgE antibodies than did the placebo member. The logarithm of the RAST units for each patient, as well as the mean IgE antibody levels for the treated and control groups, is presented in Fig. 5. Again, in this analysis the preseasonal IgE antibody levels of the patient pairs were remarkably similar (placebo $\bar{X} = 2.57$, treated $\bar{X} = 2.56$).

When the study was finished but before the code was broken, the patients were asked to complete a questionnaire assessing the treatment. Ten of the 13 patients from each group responded. The questionnaire results are summarized in Table II. The patient's acceptance of the Spinhaler as a convenient means to administer the medication was mixed. Generally those patients who obtained the greatest relief from using the medication found the Spinhaler to be an acceptable means of administering the medication, whereas those who obtained no relief found it to be inconvenient to use and carry.

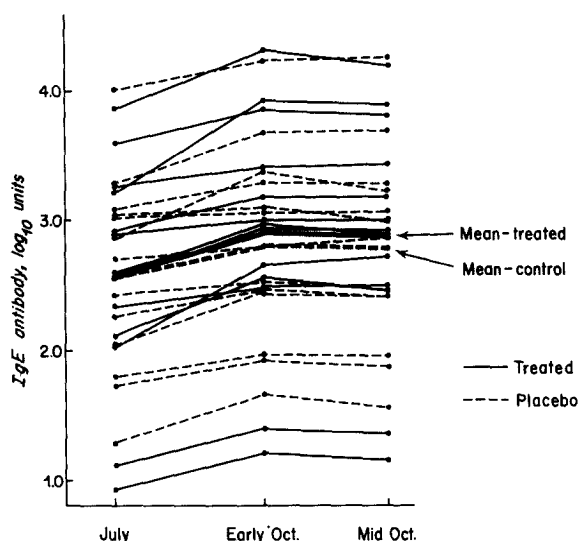


FIG. 5. IgE levels in each patient determined by RAST. Preseasonal July value, 2 post-seasonal October values. Results recorded as log₁₀ RAST units. (Serum from a nonallergic control had essentially no reactivity, 0.05% of counts added were bound.)

TABLE II. Analysis of questionnaire results

	Placebo	Treated
No. of patients responding	10	10
Patient rating		
Beneficial	5	8
Extreme	1	4
Moderate	3	3
Slight	1	1
No benefit	5	2
Compared to last yr, symptoms were		
Better	4	5
No better	6	5
If available, would use treatment next yr	5	8

DISCUSSION

In this study we have analyzed the effects of cromolyn sodium in the treatment of ragweed hay fever and on the production of IgE antibodies in response to pollen exposure. The results suggest that cromolyn sodium was significantly effective in relieving the symptoms of ragweed pollinosis in patients with high preseasonal levels of ragweed antibody, whereas in patients with lower IgE antibody levels its effectiveness could not be established. In particular, this reduction of symptom severity was seen in treated patients whose preseasonal IgE antibody RAST values were above 5.0%. Other studies have produced variable results, with some groups claiming significant beneficial effects of treating seasonal allergic rhinitis with cromolyn sodium,^{14, 16-18, 29, 30} whereas others have found that it does not significantly reduce hay fever symptoms.¹⁵ However, the observation that patients with high IgE antibody levels were those

who experienced a significant reduction of hay fever symptoms may give some indication as to which patients should receive cromolyn sodium for treatment of ragweed hay fever. Bernstein and associates⁴ found that patients under 17 yr of age demonstrated a more marked treatment effect from cromolyn sodium than did patients older than 17 yr.⁴ Gleich and Yunginger³¹ have found that levels of IgE antibody to ragweed are inversely correlated with age. It is therefore possible that those patients of Bernstein's who showed a beneficial treatment effect may have had relatively higher IgE antibody levels as compared to the whole group.

Rises in IgE antibody levels following pollen exposure were significantly greater in the treated group than in controls. This finding has been reported previously by Berg and Johansson³² and may mean: (1) that cromolyn sodium acts in some way to directly stimulate IgE production or (2) that cromolyn sodium effectively reduces the symptoms of hay fever so that the treated patients can tolerate a higher level of pollen exposure, and as a function of greater pollen exposure, the IgE levels rise to a greater degree. Engstrom³³ has demonstrated that tolerance to allergen challenge in children with seasonal allergic rhinitis can be significantly increased by prophylactic intranasal administration of cromolyn sodium. As symptoms are absent or reduced in the treated patients, they may possibly be exposed to larger amounts of pollen allergen during a pollen season than the untreated patients, causing the average increase of reaginic activity to be relatively higher.

Because of the inconvenience of administering cromolyn sodium powder with a Spinhaler, some experimental work has been done with a 2% and 4% solution of cromolyn sodium delivered to the nose with a spray bottle. Preliminary evidence suggests that this is a convenient and effective means of administration.³⁴⁻³⁶ However, comparisons of trials with cromolyn sodium both as a 2% solution and in powder form suggest that nasal insufflation of cromolyn sodium powder may be more effective in treating allergic rhinitis than nasal administration of cromolyn as a solution.³⁶ As in studies with cromolyn sodium powder, some trials have failed to demonstrate that solutions of cromolyn sodium are significantly better than placebo in controlling symptoms of allergic pollinosis.^{37, 38}

Additional studies seem warranted to determine if high preseasonal IgE antibody levels serve as useful predictive factors for beneficial results in treating seasonal allergic rhinitis with cromolyn sodium and to determine if cromolyn sodium affects IgE antibody formation in asthmatics receiving cromolyn therapy.

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