

Disodium cromoglycate in ragweed-allergic rhinitis

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This study was designed to test the effectiveness of disodium cromoglycate when compared to placebo in a double-blind study in patients with ragweed allergic rhinitis. Patients were selected on the basis of a clinical history and a 4+ reaction to the intradermal injection of water-soluble ragweed, 0.02 c.c. of 500 PNU/c.c. Active agent/placebo groups were selected at random and were on the drug for approximately 8 wk, commencing 1 wk prior to the onset of the ragweed pollen season. Patient response was evaluated using patient diary cards, number of antihistamine tablets taken, and patient interviews. In the Toronto study, of 17 patients on the active drug, 15 were graded as improved, compared to only 6 of 21 placebo-treated patients who were improved. However, in the Hamilton study, results were less impressive. Nonetheless, it appears that intranasal insufflation of disodium cromoglycate was more effective in reducing ragweed hay fever symptoms than placebo.

The main therapeutic action of disodium cromoglycate (DSCG) is thought to be its inhibitory effect on the release of the mediators of type 1 anaphylactic hypersensitivity reactions from sensitized mast cells.¹ Taylor and associates² have presented evidence to suggest that DSCG inhibits mast cell degranulation by its ability to block cyclic adenosine monophosphate (AMP) phosphodiesterase activity.

DSCG has been used for some years in the treatment of asthma, mainly in the United Kingdom and in Europe and more recently in North America.^{3, 5} While it appeared at first that those patients who have allergic mechanisms causing asthma would be the most suitable candidates for DSCG, some patients without a clear picture of allergy also responded well, while some patients who appeared to be clearly "allergic" appeared not to do so.⁶

In the last few years, several reports have suggested that intranasal insufflation of DSCG helped to control nasal allergy symptoms due to grass pollen.^{7, 8} Recently, the drug was shown to be effective and safe in the treatment of perennial allergic rhinitis.⁹ We mounted a double-blind cross-over trial using DSCG in a dose of one 5-mg capsule inhaled into each nostril 4 times daily during the 1973 ragweed season, using lactose powder as a placebo control. Our results were inconclusive.

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Since it was felt that the dose of DSCG may have been inadequate, a further trial was carried out in two centers, Toronto and Hamilton, during the ragweed pollen season in 1974. In both studies the dose of DSCG was 10 mg per capsule, propelled by a bulb syringe into each nostril 4 times a day in a double-blind manner, again using lactose powder as the control agent.

MATERIALS AND METHODS

Patients for the trial were recruited from our practices. All were allergic to ragweed pollen (*Ambrosia elatior*) by history (hay fever symptoms during the ragweed pollen season) and by having a strongly positive intradermal or prick skin test reaction with wheal-and-flare response to a challenge of 0.02 c.c. of an aqueous ragweed pollen extract containing 500 PNU/c.c. Patients with large nasal polyps and/or chronic nasal or sinus infection were not included in the study. Informed consent was obtained in all patients entering the study.

Patients were assigned in a random fashion by the hospital pharmacies to either the placebo or the active treatment group. Neither the physician nor the patient was aware of the assignment. There was no attempt at crossover between active material and placebo. Each patient had a complete physical examination prior to the allergy season, and was instructed in the use of the bulb syringe apparatus which propelled the white powder from a clear plastic capsule into each nostril. The drug containing capsules and bulb syringe apparatus was supplied by Fisons Ltd., Toronto, Ontario, Canada. Patients were instructed to start the treatment one week prior to the anticipated ragweed pollen season, which usually starts in this area about August 15, since the mechanism of action of DSCG is thought to be prophylactic.

Each patient completed a questionnaire regarding his allergic history prior to entry into the study, and was asked to fill out a detailed diary card daily over an 8- to 10-wk period. They were asked to record symptoms, including the number of sneezing episodes, the degree of nasal obstruction, the degree of watery rhinorrhea, itching of the eyes and nose, sinus pain, and the general feeling of well-being. Patients were interviewed either personally or by telephone every 2 wk and examined every 4 wk during the trial. They were asked to comment on the degree of relief from the drug treatment. They were then classed as very good, good, or poor responders.

Antihistamine tablets (4 mg chlorpheniramine) were supplied and the patient was asked to record the number of antihistamine tablets taken daily for allergic symptoms. Pollen counts for ragweed were recorded daily in Toronto and Hamilton, which are 35 miles apart, with a Hirst automatic volumetric spore trap operating 24 hr each day. All other drugs usually taken, such as corticosteroids, methyl xanthines, and beta agonists for asthma, were continued and recorded.

Antiragweed IgE antibody levels were measured by the RAST method (Pharmacia, Montreal), and were determined prior to, during and after the pollen season. They were scored according to the following scale recommended by the supplier: 4, highly positive; 3, strongly positive; 2, clearly positive; 1, borderline; and 0, negative. Patients in the Hamilton study group, but not in the Toronto study group, were matched for antiragweed IgE RAST scores.

RESULTS

Patients from the two groups were studied separately. There were 38 patients in the Toronto study. Seventeen were on the active drug and 21 on placebo. There were 39 patients in the Hamilton study, 19 on active drug and 20 on placebo, ranging from 10 to 59 yr. Age ranges in the two studies were similar. There were 16 males and 22 females in the Toronto group and 13 males and 26 females in the Hamilton group. Groups were reasonably matched for age, sex, and duration of symptoms (Table I).

Most patients filled out their diary cards and persisted with the trial for the whole period. Patients in the Hamilton group started their records 1 wk before

TABLE I. Description of active and placebo group

	No.	Ages (yr)	M/F	Days/pt.
<i>Toronto</i>				
Active	17	10-59	8/9	34
Placebo	21	14-52	8/13	32
<i>Hamilton</i>				
Active	19	14-47	4/15	61
Placebo	20	16-53	9/11	54

TABLE II. Subjective evaluation in total patient group

	Active		Placebo	
	No.	%	No.	%
<i>Toronto</i>				
Very good	11	65	3	14
Good	4	24	3	14
Poor	2	11	15	72
Total	17	100	21	100
		(p < 0.001; $\chi^2 = 11.22$)		
<i>Hamilton</i>				
Very good	3	16	0	0
Good	7	42	6	30
Poor	9	42	14	70
Total	19	100	20	100
		(p < 0.05; $\chi^2 = 3.08$)		

the Toronto group, i.e., 2 wk prior to the pollen season. The mean duration of the study period was similar for both active and placebo groups. The number of antihistamine tablets consumed was not significantly different for the active and the placebo groups. Analysis of the diary score cards showed that patient symptoms followed the appearance of airborne ragweed pollen. In general, the mean daily pollen count was higher in the Hamilton area compared to Toronto. (Hamilton: Maximum, 673; mean, 82. Toronto: maximum, 310, mean, 78.)

Statistical analysis of symptom scores failed to detect significant differences between active and placebo groups. This could have been due to the wide variation in symptom scores in both groups. (Mean symptom score, active ($\pm 1SD$) = 10.5 ± 8.0 ; Mean symptom score, placebo ($\pm 1SD$) = 15.4 ± 10.6 .)

In contrast, subjective evaluation (interview) of patient responses revealed significant differences between active drug and placebo, particularly in the Toronto study. The number of patients helped by the DSCG powder in the Toronto groups was 15 of a total of 17, compared to those helped by placebo, which was 6 of 21 (p < 0.001) with a χ^2 value of 11.22. In the Hamilton study, the results were less conclusive: 10 of 19 were helped by the DSCG and 6 of 20 by the placebo (p < 0.05, $\chi^2 = 3.08$) (Table II). Several patients dropped out early in the study when it was apparent that they were getting no relief from the treatment. All of these are included in the "poor" result group. Most of these patients were on placebo.

The groups were broken down further to assess other factors which might have contributed to the results. The Toronto group was divided into those with

TABLE III. Subjective evaluation in patients receiving ragweed hyposensitization

	Active		Placebo	
	No.	%	No.	%
<i>Toronto</i>				
Improved (V. G. and G.)	12	100	5	33
Not improved	0	0	10	67
Total	12	100	15	100
<i>Hamilton</i>				
Improved	4	67	1	16
Not improved	2	33	5	84
Total	6	100	6	100

TABLE IV. Subjective evaluation in patients not receiving hyposensitization

	Active		Placebo	
	No.	%	No.	%
<i>Toronto</i>				
Improved	3	60	0	0
Not improved	2	40	6	100
Total	5	100	6	100
<i>Hamilton</i>				
Improved	6	46	5	36
Not improved	7	54	9	64
Total	13	100	14	100

antiragweed IgE RAST scores greater or less than 1. In those with scores greater than 1, the success rate for the relief of symptoms was 14 of 16 in the active group and fell to 3 of 16 for the placebo group. This result ($p < 0.0005$) is highly significant, indicating that those patients with higher RAST scores for IgE antibody were helped to a greater degree, perhaps because their symptoms were triggered more specifically by the allergic reaction.

Many patients in the study were on a program of hyposensitization with aqueous ragweed extract. They were told to continue with this program. In the Toronto group all 12 patients receiving hyposensitization against ragweed and DSCG powder were improved, compared to 5 of 15 patients who received hyposensitization and placebo powder. The figures for the Hamilton group show that 4 of 6 on hyposensitization and DSCG were improved, compared to 1 of 6 on hyposensitization plus placebo (Table III).

Since none of the patients in the Hamilton group had RAST scores <1 , and the majority had RAST scores >2 , a similar analysis of the Hamilton patients was not possible.

In patients not receiving hyposensitization against ragweed, 3 of 5 taking active drug in the Toronto group and 6 of 13 in the Hamilton group were improved, while none of 6 in the Toronto placebo-treated group and 5 of 14 in the Hamilton placebo-treated group were improved (Table IV).

In the Toronto group, more detailed statistical analysis was done comparing hyposensitization alone, active drug treatment alone, and active drug plus hyposensitization. These data revealed that all modes of treatment lead to subjective

improvement. The hyposensitization effect was significant ($p < 0.05$), the active drug effect was highly significant ($p < 0.0001$), and the interaction effect between active drug and hyposensitization was also significant ($p < 0.025$). Statistical analysis of the Hamilton data gave a χ^2 value of 0.33 and failed to reveal an improvement on active drug or on hyposensitization even on a subjective basis.

Side effects from the use of either powder were minimal. They included increased sneezing, cough, and occasional headache occurring in only a few patients. The sneezing and coughing appeared to be more prevalent in the placebo-treated group, while headache was more frequent in the DSCG-treated group.

DISCUSSION

DSCG is a unique pharmacologic agent whose main action appears to be the inhibition of release of chemical mediators from tissue mast cells sensitized by specific IgE after antigen challenge.¹⁰

The object of these studies was to determine whether nasal insufflation of DSCG powder was effective in the symptomatic treatment of ragweed-allergic rhinitis. When patient symptom scores were subjected to statistical analysis, there was no significant difference between active and placebo groups. The difficulty in obtaining objective assessment of patient symptoms on a daily basis over many weeks is well recognized. Nevertheless, it was striking that subjective evaluation by the patient showed marked differences in the active- and placebo-treated groups in the Toronto study, and some differences, although not statistically significant, in the Hamilton study. The decreased effectiveness of the DSCG in the Hamilton group of patients may have been related to higher pollen counts in that area, or to patient selection, since more of the Hamilton patients had asthma (16 of 39), both "extrinsic" and "intrinsic," than the Toronto group (12 of 38), most of whom had milder asthma, mostly exercise-induced and only rarely associated with the ragweed season.

Despite the lack of statistically significant differences in the Hamilton group between active and placebo materials, more patients felt they were helped by the active treatment (52%) than by placebo treatment (30%). It appears that hyposensitization with ragweed pollen extract may have acted in a synergistic fashion in those patients receiving both treatments.

Overall, we have concluded from these studies that disodium cromoglycate powder given in a dose of 10 mg into each nostril 4 times daily prior to and during the ragweed pollen season may be more effective in controlling symptoms of ragweed-allergic rhinitis in some patients than a lactose placebo.

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REFERENCES

- 1 Cox, J. S. G.: Disodium cromoglycate: A specific inhibitor of reaginic antibody-antigen mechanisms, *Nature* **216**: 1328, 1967.
- 2 Taylor, W. A., Francis, D. H., Sheldon, D., and Roitt, I. M.: Anti-allergic actions of

- disodium cromoglycate and other drugs known to inhibit cyclic 3'5'-nucleotide phosphodiesterase, *Int. Arch. Allergy Appl. Immunol.* 47: 175, 1974.
- 3 Pepys, J., Hargreave, F. E., Chan, M., and McCarthy, D. S.: Inhibitory effects of disodium cromoglycate on allergen-inhalation tests, *Lancet* 2: 134, 1968.
 - 4 Silverman, M., and Turner-Warwick, M.: Exercise induced asthma: Response to disodium cromoglycate in skin-test positive and skin-test negative subjects, *Clin. Allergy* 2: 137, 1972.
 - 5 Kolotkin, B. M., Lee, C. K., and Townley, R. G.: Duration and specificity of sodium cromolyn on allergen inhalation challenges in asthmatics, *J. ALLERGY CLIN. IMMUNOL.* 53: 288, 1974.
 - 6 Toogood, J. H., McCourtie, D. R., Jennings, B. H., Lefocoe, N. M., and Mullin, J. K.: Changes in corticosteroid usage by chronic asthma patients during a year of cromoglycate treatment, *J. ALLERGY CLIN. IMMUNOL.* 52: 334, 1973.
 - 7 Taylor, G., and Shivalkar, P. R.: Disodium cromoglycate: Laboratory studies and clinical trial in allergic rhinitis, *Clin. Allergy* 1: 189, 1971.
 - 8 Holopainen, E., Backman, A., and Salo, O.: Effects of disodium cromoglycate on seasonal allergic rhinitis, *Lancet* 1: 55, 1971.
 - 9 Blair, H., and Viner, A. S.: A double blind trial of a 2% solution of sodium cromoglycate in perennial rhinitis, *Clin. Allergy* 5: 139, 1975.
 - 10 Goose, J., and Blair, A. M. J. N.: Passive cutaneous anaphylaxis in the rat, induced with two homogeneous reagin-like antibody sera and its specific inhibition with disodium cromoglycate, *Immunology* 16: 749, 1969.