

Treatment of ragweed hay fever with intranasally administered disodium cromoglycate*

S. CRAIG, E. RUBINSTEIN, R. E. REISMAN
and C. E. ARBESMAN

*Allergy Research Laboratory, Buffalo General Hospital, and Departments of
Medicine and Microbiology, State University of New York at Buffalo*

Summary

In a double-blind study the therapeutic effect of a 4% disodium cromoglycate (DSCG) nasal solution was evaluated in thirty-nine patients with acute symptoms of ragweed hay fever. Patients were randomly assigned to the DSCG or placebo group as they presented with allergic rhinitis. Overall, the DSCG was not more effective than placebo in controlling the symptoms of rhinitis or in decreasing the need for concomitant antihistamines or corticosteroids. Among patients with the highest pre-treatment serum ragweed-specific IgE (RW IgE) levels, drug-treated patients had some reduction in symptoms as compared to their placebo controls during the peak of the ragweed pollen season. DSCG treatment did not influence the usual seasonal rise in RW IgE. Side effects from both the active and placebo aerosols were frequent but mild.

We conclude that DSCG nasal solution used for the treatment of seasonal ragweed allergic rhinitis is relatively ineffective.

Introduction

Disodium cromoglycate (DSCG) has been found beneficial in the treatment of allergen-induced asthma (Bernstein *et al.*, 1971; Blumenthal *et al.*, 1973; Falliers, 1975; Irani *et al.*, 1972; Smith & Devey, 1968; Toogood *et al.*, 1971). Subsequently it was adapted and administered as an intranasal medication for therapy of allergic rhinitis, with conflicting therapeutic results (Leiferman *et al.*, 1975; Kuhn *et al.*, 1976; Wüthrich, 1974; Mygind, Hansen & Jorgensen, 1972; Engstrom *et al.*, 1971; Blair & Viner, 1975; Girard & Bertrand, 1975; Holopainen *et al.*, 1975; Blair & Herbert, 1973; Mannes & Ezeoke, 1973; Tuffiash & McLean, 1975). The purpose of this double-blind study

* This paper was presented in part at the 32nd annual meeting of the American Academy of Allergy, San Juan, Puerto Rico, March 1976.

Correspondence: Dr Robert E. Reisman, Allergy Research Laboratory, Buffalo General Hospital, 100 High Street, Buffalo, N.Y. 14203, U.S.A.

was to assess the effectiveness of a 4% DSCG solution in alleviating the nasal symptoms of ragweed hay fever. The DSCG was administered with the onset of acute symptoms.

Materials and methods

Selection of patients

Patients with acute symptoms of ragweed hay fever were selected for this study. The diagnosis was confirmed by history, physical examination and skin test reaction. Patients receiving immunotherapy (IT) were included. The only criteria for exclusion of patients from the study were: (a) the use of cromolyn for asthma; (b) systemic steroid therapy; (c) pregnancy; and (d) age less than 12 years.

Therapy

In a random, double-blind method, patients were assigned either the active drug (4% DSCG, 0.01% EDTA, 0.01% benzalkonium chloride) or the placebo (0.01% EDTA, 0.01% benzalkonium chloride). They were instructed to administer one spray of the metered-dose nebulizer into each nostril six times per day (every 3 hr during waking hours only). Each dose delivered 5.2 mg of DSCG. Patients were to use 4 mg chlorpheniramine tablets or similar antihistamines if needed. Therapy was initiated only when patients presented with the acute symptoms of ragweed hay fever.

Evaluation

Clinical. Patients were interviewed and examined by one of the physicians at bi-weekly intervals during their 6 week therapeutic course. Each patient kept a symptom diary modified slightly from that used by Norman, Rhyne & Mellits (1966). The following specific symptoms were recorded: running nose; stuffy nose; eye irritation; number of sneezing episodes; and number of noseblowing episodes. These were scored on a 0–4 scale. Day-time and night-time symptoms were recorded separately. All medications were tabulated in the diary, and each antihistamine tablet ingested was assigned a score of 1. Any side effect of the medication was also recorded. At the end of the study the patients and the physicians independently assessed the clinical results, without knowledge of the type of therapy.

Daily ragweed pollen counts were determined by the roto-slide method (Ogden & Raynor, 1967).

Immunological. Serum samples obtained at the beginning and at the end of the study were analyzed for ragweed-specific IgE (RW IgE) by the radioallergosorbent test (RAST) (Ceska, Eriksson & Varga, 1972; Reisman, Wypych & Arbesman, 1975). The initial serum sample was obtained when patients were first seen with acute hay fever. The follow-up serum was taken about 1st October, at the end of the pollen season. The results were expressed as a percentage of a known positive serum pool standard. Levels greater than 5% were considered significant.

Results

Clinical

Seventy-one patients were initially enrolled in the study. Thirty-nine of these patients completed the 4–6 week course. Of the thirty-two 'drop-outs', nine patients were non-compliant. Nine patients had a low pre-treatment serum level of RW IgE (<5%) and

thus questionable sensitivity to ragweed. Fourteen patients developed severe symptoms of ragweed rhinitis and were removed prematurely from the study because they required systemic corticosteroids for the relief of their symptoms. They were considered 'early treatment failures'. Five of these patients were using the DSCG spray and nine the placebo.

Analysis of the symptom diaries of all patients who used the assigned drug (except patients with non-detectable RW IgE) revealed no significant difference in mean total symptom scores between the DSCG- and placebo-treated groups (Fig. 1). Symptom scores were slightly lower in the DSCG-treated group during the peak season but this difference was not statistically significant.

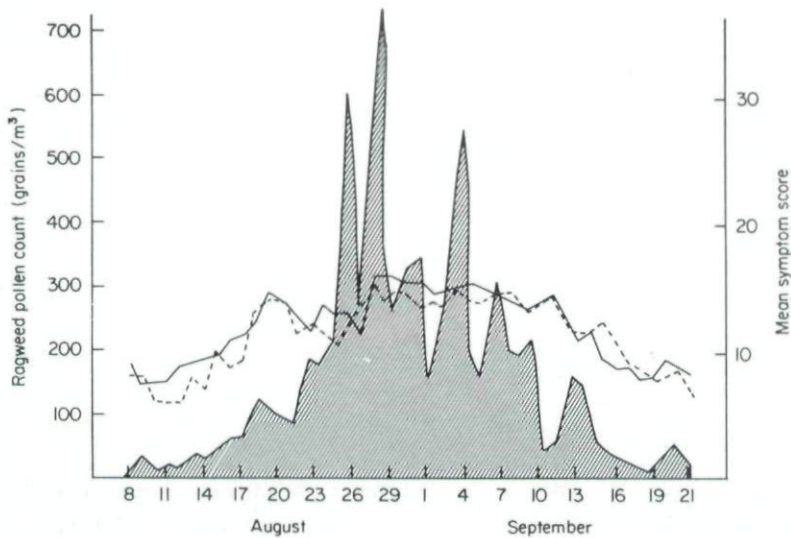


Fig. 1. Group mean daily symptom scores for all DSCG and placebo patients who used the assigned drug as prescribed. Only the patients with negative initial RAST values are excluded. There is no statistical difference between the two groups ($P > 0.1$ by Students *t*-test). (---) DSCG; (—) placebo; (▨) shows ragweed pollen count.

Of the thirty-nine patients who completed the original protocol, twenty-two patients received the DSCG and seventeen the placebo. Clinical characteristics of the placebo and DSCG groups are shown in Table 1. The early treatment failure group was added for statistical analysis (Table 2). There was no significant benefit of the DSCG as assessed by symptom scores or by the patients' evaluation. There was a trend in favour of the DSCG according to the physicians' evaluation, $P = 0.058$ by Fisher's exact test. Each group used approximately the same number of adjunctive antihistamine tablets per patient per day.

Clinical relevance of RW-specific IgE

In the non-steroid-treated group of thirty-nine patients, the mean initial serum RW IgE level and subsequent seasonal change were similar in the DSCG- and placebo-treated groups. The mean initial serum RW IgE of the DSCG group was 107% while that of the placebo group was 74.9%; the difference between these mean values was

Table 1. Analysis of patients in this study

Treatment	No. of Patients	Age		Sex (M/F)	RW IgE (%) [*]		Immunotherapy
		Range	Mean		Initial	Final	
DSCG	22	12-44	23.9	11/11	107.4	147.6†	7
Placebo	17	12-31	20.0	11/6	74.9	110.2	4

^{*} Ragweed-specific IgE levels are expressed as a percentage of a positive serum control.

† This is the mean value of the twenty DSCG-treated patients for whom final RW IgE values were obtained.

Table 2. Clinical effectiveness of nasal DSCG *vs* placebo

Clinical improvement [*]	DSCG	Placebo
Mean symptom scores	13.9	14.6
Patients' evaluation	12/25†	9/26
Physicians' evaluation	11/27	5/26

^{*} This includes the original thirty-nine patients plus fourteen patients who required steroid therapy.

† Two of the cromolyn-treated patients did not complete the questionnaire.

not statistically significant ($P > 0.05$, Student's *t*-test). The mean serum RW IgE increase was 40% in the DSCG group and 36% in the placebo group (Table 1).

When patients with high initial serum RW IgE levels (greater than 80%) were studied separately, there was a suggestion of drug effect. Within this group the drug-treated patients were significantly improved by analysis of mean daily symptom scores when compared with the high-RAST placebo group. Although physicians' and patients' evaluations also suggested improvement in this drug-treated group, these results were not statistically significant (Table 3).

In contrast to this apparent predictive value of the initial RW IgE levels is the fact that the DSCG-treated patients with the most severe symptoms, i.e. those in the 'early treatment failure' group, had a mean initial RW IgE of 118%, which is comparable to the 107.4% mean of the DSCG-treated patients able to complete the study. The mean initial RW IgE was 90% for the placebo patients in the 'early treatment failure' group. Thus it is unclear that a high pre-season RW IgE level can predict success with DSCG.

Side effects of medication

41% of the patients reported minor side effects from the assigned spray (Table 4), although in no instance were the side effects so severe as to require termination from the study. The most frequent side effects were sneezing, nasal burning and increased rhinorrhoea.

Table 3. Clinical results in patients with pre-treatment serum ragweed-specific IGE levels greater than 80%

Therapy	No. of patients	Peak season mean symptom score*	Patients improved	
			Patients' evaluation	Physicians evaluation
DSCG	19	13.7	8†	9
Placebo	11	17.0	2‡	2§

* These values are the group mean symptom score for the 2 week peak of the ragweed season. The group differences are significant with a P value of 0.01. The results of drug and placebo treatment, as determined by patients' and physicians' evaluations, did not show a statistical difference (Fisher's exact test: for physicians' evaluation, $P = 0.12$; for patients' evaluation, $P = 0.21$).

† Two DSCG-treated patients did not submit the final evaluation form.

‡ Three placebo-treated patients did not submit the final evaluation form.

§ Insufficient data to make the final evaluation of one patient.

Table 4. Side effects of the nasal sprays

Side effect	DSCG spray ($n = 33$)*	Placebo spray ($n = 37$)
Nasal burning	5	13
Sneezing	8	9
Pharyngeal burning	2	1
Rhinorrhoea	3	2
Increased nasal stuffiness	0	1
Headache	1	0

* One DSCG patient did not return for follow-up.

Five patients (7%) complained that the spraying apparatus was inconvenient to carry.

Discussion

In this study there was no dramatic relief of the symptoms of ragweed hay fever by intranasal sodium cromolyn. Treated and placebo groups could not be differentiated by analysis of three indices: (a) group mean symptom scores; (b) patients' evaluation; and (c) physicians' evaluation. There was also no reduction of adjunctive antihistamine use in the DSCG group, and no reduction in the number of patients requiring steroids to control their symptoms.

The method of symptom scoring used in this study has been shown to reliably reflect clinical sensitivity, correlating well with the degree of *in vitro* histamine release from leucocytes (Norman *et al.*, 1966; Lichtenstein *et al.*, 1966). Since eye symptoms might not be expected to be affected by this form of therapy, symptom scores were recalculated omitting this parameter. There was no change in the results.

In the present study treatment was initiated after clinical symptoms of ragweed

hay fever had commenced. In studies by other investigations, DSCG treatment was started before the onset of the ragweed season. We believe that the present approach reflects a more practical method of administering therapy. Although patients may have had ragweed hay fever symptoms in previous years, one cannot predict that symptoms will occur the next year.

Two recent studies have suggested that the effect of DSCG and placebo treatment could be differentiated by selecting patients on the basis of pre-season RW IgE levels (Liefberman *et al.*, 1975; Kuhn *et al.*, 1976)*. The present study only partially supports this suggestion. Among patients with high RW-specific IgE (>80%), the DSCG-treated group had a reduction of 19% of total symptom scores as compared with placebo controls during the peak 2 weeks of pollination. Over the entire ragweed season, however, there was no significant difference in the symptom scores of the drug- and placebo-treated patients ($P > 0.1$, Student's *t*-test). There was no significant improvement according to patients' and physicians' evaluations (Table 3). In addition, the patients in the 'early treatment failure' group had similar mean initial RW IgE values as those in the 'final study group'. It is thus uncertain whether there is any clinical relevance of separating patients on the basis of initial RW IgE. Theoretically, one might expect the DSCG to be more effective in the patients with lesser sensitivity.

There are conflicting reports concerning the enhancement of the seasonal rise of specific IgE (Liefberman *et al.*, 1975; Wüthrich, 1974) by DSCG. In the present study there was no enhancement of RW IgE production by DSCG treatment.

Double blind studies employing various DSCG nasal preparations for the treatment of seasonal and perennial rhinitis have yielded conflicting results (Liefberman *et al.*, 1975; Kuhn *et al.*, 1976; Wüthrich, 1974; Mygind *et al.*, 1972; Engstrom *et al.*, 1971; Blair & Herbert, 1973; Manners & Ezeoke, 1973; Tuffiash & McLean, 1975). Close analysis of these studies indicate that, at best, DSCG is only a moderately effective medication.

Nasal challenge experiments suggested that DSCG is effective in preventing allergen-induced increased nasal obstruction (Taylor, 1974). A possible reason for the difference in the results of the nasal challenge studies and the clinical studies could be the fact that natural antigenic challenge is large and continuous, rather than dose-controlled and timed. In the clinical situation the nasal priming effect may enhance the patient's sensitivity to a relatively small antigenetic challenge (Connell, 1969). Also rhinorrhoea, a common symptom, might wash the drug from the nose before it has time to be effective.

In general, no significant benefit of the 4% DSCG nasal spray was demonstrated in the ongoing treatment of ragweed hay fever. No patient was strongly favorably impressed by the drug, nor did any patient request the drug for future use. Certainly the results indicate that the clinical effectiveness of intranasally administered DSCG are not as clear-cut as DSCG intrabronchial administration for the prevention of ragweed pollen asthma.

Acknowledgments

This paper is dedicated to Dr Felix Milgrom of the New York State University, Buffalo, on the occasion of the 30th anniversary of his research activities.

* The initial RW IgE value for the patients in this study is not a true pre-seasonal value because the initial serum sample was obtained after the patients had begun to have symptoms.

This study was supported in part by United States Public Health Service Research Grant 5 RO1 AI 01303 of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

This study was also supported in part by Fisons Corporation, Bedford, Massachusetts.

References

- BERNSTEIN, I.L., BRANDON, M.L., BROWN, E.B., EVANS, R.R., FEINBERG, A.R., FRIEDLAENDER, S., HADLEY, R.A., HANDELMAN, N.I., KRUMHOLZ, R.A., SIEGEL, S.C., THURSTON, S.L. & YAMATE, M. (1971) A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy. *Journal of Allergy and Clinical Immunology*, **47**, Abstract, 95.
- BLAIR, H. & HERBERT, R.L. (1973) Treatment of seasonal allergic rhinitis with a 2% sodium cromoglycate (BP) solution. *Clinical Allergy*, **3**, 283.
- BLAIR, H. & VINER, A.S. (1975) A double-blind trial of a 2% solution of sodium cromoglycate in perennial rhinitis. *Clinical Allergy*, **5**, 139.
- BLUMENTHAL, M.N., SCHOENWETTER, W.F., MACDONALD, F.M. & MCHUGH, R.B. (1973) Cromolyn in extrinsic and intrinsic asthma. *Journal of Allergy and Clinical Immunology*, **52**, 105.
- CESKA, M., ERIKSSON, R. & VARGA, J.M. (1972) Radioimmunosorbent assay of allergens. *Journal of Allergy and Clinical Immunology*, **49**, 1.
- CONNELL, J.T. (1969) Quantitative intranasal pollen challenges. III. The priming effect in allergic rhinitis. *Journal of Allergy*, **43**, 33.
- ENGSTROM, I., OBERGER, E., BLYCKERT, A. & KRAEPELIN, S.L. (1971) Disodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children. *Annals of Allergy*, **29**, 505.
- FALLIERS, C.J. (1975) Cromolyn sodium (Disodium cromoglycate) prophylaxis. *Pediatric Clinics of North America*, **22**, 141.
- GIRARD, J.P. & BERTRAND, J. (1975) Study of 2% solution of sodium cromoglycate in perennial rhinitis assessed by subjective and objective parameters. *Clinical Allergy*, **5**, 301.
- HOLOPAINEN, E., VINER, T., BACKMAN, A., SALO, O., HANNUKSELA, M. & MALMBERG, H. (1975) Clinical trial of a two per cent solution of DSCG on perennial rhinitis. *Acta Allergologica*, **30**, 216.
- IRANI, F.A., JONES, N.L., GENT, M. & NEWHOUSE, M.T. (1972) Evaluation of disodium cromoglycate in intrinsic and extrinsic asthma. *American Review of Respiratory Disease*, **106**, 179.
- KUHN, F., LINDSAY, D., KOORS, P., MOYER, R., HANDELMAN, N., SCHWARTZ, H., NAGEL, J., ROSCH, J., MURPHEY, S., MILLER, L. & FRIDAY, G. (1976) Cromolyn sodium (CS) nasal solution in the treatment of ragweed allergic rhinitis. *Journal of Allergy and Clinical Immunology*, **57**, 241.
- LEIFERMAN, K.M., YUNGINGER, J.W., LARSON, J.B. & GLEICH, G.J. (1975) The effect of cromolyn sodium powder as a treatment for ragweed pollinosis. *Journal of Allergy and Clinical Immunology*, **56**, 481.
- LICHTENSTEIN, L.M., NORMAN, P.S., WINKENWERDER, W.L. & OSLER, A.G. (1966) *In vitro* studies of human ragweed allergy: changes in cellular and humoral activity associated with specific desensitization. *Journal of Clinical Investigation*, **45**, 1126.
- MANNERS, B. & EZEKE, A. (1973) Serum IgE levels and the use of sodium cromoglycate (BP) in hay fever: a study of forty-six patients from a single general practice. *Clinical Allergy*, **3**, 311.
- MYGIND, N., HANSEN, I.B. & JORGENSEN, M.B. (1972) Disodium cromoglycate nasal spray in adult patients with perennial rhinitis. *Acta Allergologica*, **27**, 372.
- NORMAN, P.S., RHYNE, M.B. & MELLITS, E.D. (1966) The evaluation of agents for the treatment of seasonal respiratory allergies. *International Encyclopedia of Pharmacology and Therapeutics* (ed. L. Lasagna) Vol. 2, p. 639. Pergamon Press, New York.
- OGDEN, E.C. & RAYNOR, G.S. (1967) A new sampler for airborne pollen: The roto-slide. *Journal of Allergy*, **40**, 1.
- REISMAN, R.E., WYPYCH, J.I. & ARBESMAN, C.E. (1975) Relationship of immunotherapy, seasonal pollen exposure and clinical response to serum concentrations of total IgE and ragweed-specific IgE. *International Archives of Allergy and Applied Immunology*, **48**, 721.
- SMITH, J.M. & DEVEY, G. (1968) A clinical trial of cromoglycate in the treatment of asthma in children. *British Medical Journal*, **2**, 340.

- TAYLOR, G. (1974) The nose as a model for the study of respiratory tract allergic disease. *Annals of the New York Academy of Science*, **221**, 117.
- TOOGOOD, J.M., LEFCOE, N.M., ROSE, D.J. & MCCOURTIE, D.R. (1971) A double-blind study of disodium cromoglycate for prophylaxis of bronchial asthma. *American Review of Respiratory Disease*, **104**, 323.
- TUFFIASH, W.A. & MCLEAN, J.A. (1975) A trial of 4% cromolyn sodium in seasonal allergic rhinitis. *Journal of Allergy and Clinical Immunology*, **55**, Abstract 116.
- WUTHRICH, B. (1974) Über die Wirkung einer 2%igen Lösung von Dinatrium glicicum beim Heusch-nunpfen. *Schweizerische Medizinische Wochenschrift*, **104**, 1033.

Copyright of Clinical Allergy: Journal of the British Allergy Society is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.