

Sodium cromoglycate in ragweed-allergic conjunctivitis

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Sodium cromoglycate (SCG), in a 4% solution instilled into each eye 4 times daily, was compared with placebo in a double-blind, noncrossover trial in 30 matched patients with troublesome ragweed pollen-induced conjunctivitis. In the SCG group, eye symptom scores were significantly less ($p = 0.05$), and all patients judged that their symptoms were improved over the previous year ($p < 0.05$). Less antihistamine was used by the SCG group but the difference was not significant. It was concluded that SCG was effective in the treatment of ragweed-induced seasonal allergic conjunctivitis.

Sodium cromoglycate (SCG) inhibits the antigen-induced release of mediators from sensitized tissues.¹ It has found widespread use in the treatment of asthma.² It may also be effective in the treatment of perennial³ and seasonal⁴ allergic rhinitis. An effect has been demonstrated in a number of other conditions including aphthous stomatitis,⁵ chronic proctitis,⁶ ulcerative colitis,⁷ gastritis varioliformis,⁸ gastrointestinal protein intolerance,⁹ and intestinal manifestations of systemic mastocytosis.¹⁰

Recently, Easty and associates¹¹ and Rice and Jones¹² have demonstrated the value of SCG in the treatment of vernal conjunctivitis. Kazdan and co-workers¹³ have obtained evidence of the benefit of SCG in vernal keratoconjunctivitis and allergic conjunctivitis in a noncontrolled trial. The present study is a controlled trial of locally applied SCG in seasonal allergic conjunctivitis induced by natural exposure to ragweed pollen.

MATERIALS AND METHODS

Thirty patients with allergic conjunctivitis induced by ragweed pollen were selected. They were documented with a detailed allergy questionnaire. All had had troublesome eye symptoms for at least 2 yrs in association with allergic rhinitis during the ragweed season. All had positive skin tests with ragweed pollen extract. Patients with perennial symptoms or fall seasonal symptoms which could be attrib-

uted to other allergens were excluded. None had received allergen injection treatment during the preceding 2 yr.

The study was approved by the hospital research committee. Signed informed consent was obtained for all patients entering the study.

Skin prick tests were performed with serial 10-fold dilutions of ragweed pollen extract to obtain end-point titrations. The end point was the maximum allergen dilution which elicited a wheal response larger than the control. End points varied from 2.5 to 2,500 Noon U/ml, and subjects were assigned an arbitrary sensitivity index ranging from 5 (2.5 U) to 1 (2,500 U). Patients were matched largely on the basis of end-point skin test titrations with ragweed pollen extract. Two additional factors were used in matching. Consideration was given to a subjective grading of duration of seasonal eye symptoms (2 points for conjunctivitis on all days, 2 points if symptoms lasted all day, and proportionately less points for fractions thereof). Consideration was also given to an estimate of exposure time to pollen (time in hr/wk, not spent in an air-conditioned environment). The hospital pharmacy randomly assigned one member of each pair to the SCG group and the other to the placebo group. It happened that 16 subjects were assigned to the SCG group and 14 to the placebo group. There was no crossover. The physicians and patients were informed of the treatment received by individuals only after the study was entirely completed.

The trial was started on August 16, during the first week of the ragweed pollen season in 1976. Each subject received a complete physical examination and was carefully instructed in the appropriate method of instillation of 1 drop of 4% SCG ophthalmic solution in each eye 4 times daily. Symptoms were recorded twice daily on diary cards. Eye symptoms, including redness, itchiness, tearing, and soreness, were recorded separately. Nasal symptoms, including sneezing, itch, and discharge, and cough were also recorded. The severity of symptoms was graded as: absent (0), mild (a), moderate (b), and severe (c); the duration during the day was graded: absent (0), less than 1/2 hr (1), 1/2 to

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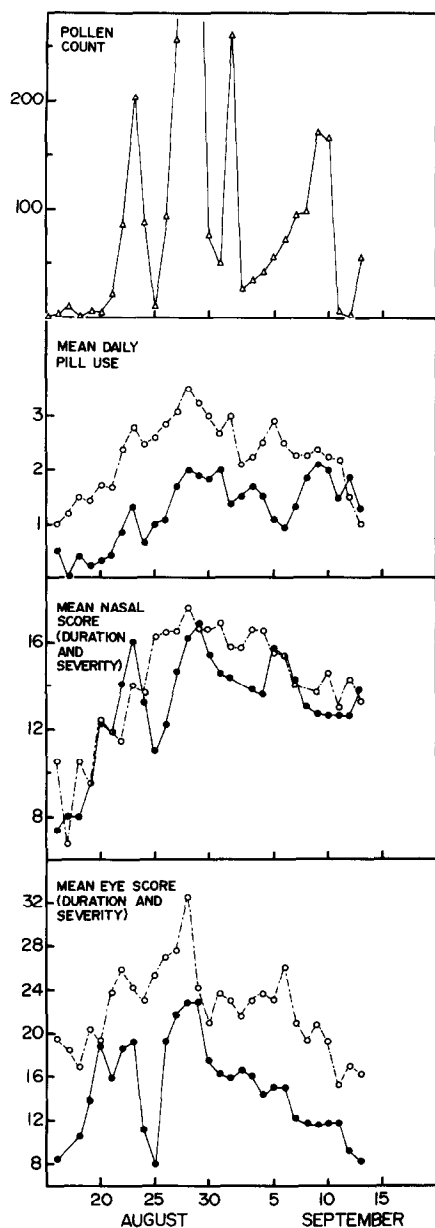


FIG. 1. The top graph indicates the mean daily ragweed pollen count. The next graph represents the mean number of antihistamine tablets taken daily (*open circles* for placebo group, *closed circles* for SCG). The next graph is a summation of scores for nasal symptoms representing both duration and severity. The bottom graph represents a summation of daily values for duration and severity of eye symptoms.

2 hr (2), and longer than 2 hr (3). Each week the patients were interviewed, the diary cards were examined, and the method of instillation of SCG was checked.

Antihistamine tablets in the form of chlorpheniramine maleate, 4 mg., were supplied. The number of tablets used was recorded. All other medication including bronchodilators and intranasal SCG were recorded. No topical eye medication except SCG was used.

At the end of the study, patients were asked whether they felt the medication they received was effective or noneffec-

TABLE I

Parameter	SCG	Placebo
Number	16	14
Sex		
Male	9	7
Female	7	7
Age range (mean)	14-52 (29)	17-51 (28)
Sensitivity index (mean)	3.5	3.7
RAST range*	1,188-17,202	1,542-17,057
RAST score (mean)	8,900	9,456
Estimated exposure time (mean)	14.6	15.4

*RAST score range for 20 nonallergic control subjects was 845 to 1,358 with a mean of 1,008.

tive, based upon a comparison with the previous year.

Symptom scores were analyzed statistically with Student's *t* test. The presence or absence of improvement in comparison with the previous year was analyzed by the χ^2 test.

The daily mean pollen counts were measured with a Hirst automatic volumetric spore trap.¹⁴

Serum concentrations of IgE antibodies to ragweed were measured by the radioallergosorbant test (RAST).¹⁵

RESULTS

Data on the 30 patients in the study are summarized in Table I. There was no significant difference between the two groups in ragweed sensitivity determined by end-point skin test titration or by RAST.

One patient with contact lenses in the SCG group could not tolerate the eye medication and left the study after one day. Another patient in the active group lost the diary card and the scores are not included. Two patients in the placebo group had severe eye symptoms and required oral prednisone. One dropped out of the study on the second day and the scores have not been included. The second patient was in the study for 10 days before the requirement for oral prednisone, and the scores for these days are included.

Daily pollen counts and symptom scores are recorded in Fig. 1. The close relationship between pollen counts and symptom scores is evident.

Patients in the SCG group used less antihistamine than did patients in the placebo group, but the difference was not significant.

Nasal symptom scores including severity and duration were similar in the two groups.

Eye symptom scores were significantly less ($p < 0.05$) in the SCG group than in the placebo group. Duration of eye symptoms was also less in the SCG group, but the difference was not significant. Total eye scores (severity and duration) were less ($p = 0.05$) in the SCG group (Fig. 1).

All 15 patients in the SCG group and 8 of 14 (57%) in the placebo group stated that they thought the medication was effective ($\chi^2 = 5.71$, $p < 0.05$).

Side effects were not marked. All patients except 2 in the SCG group and 2 in the placebo groups reported mild immediate stinging after instillation of the drops, and this was comparable in the two groups. One patient in each group noticed no stinging whatever. One patient in the placebo group noticed marked stinging but continued in the trial, and one patient with contact lenses in the SCG group experienced marked stinging and left the study after one day.

DISCUSSION

SCG in a 4% solution was effective in the treatment of ragweed-allergic conjunctivitis. The difference in the eye scores and the similarity of the nasal scores serves to highlight the local efficacy of the ophthalmic solution. Moreover, patient acceptance of the SCG ophthalmic solution and subjective reports of benefit were favorable. Improvement seemed to vary from complete loss of eye symptoms to only partial reduction in eye symptoms estimated at about 50% improvement.

The antihistamine may, to some extent, have obscured the results of the SCG since antihistamine would reduce eye symptoms as well as nasal symptoms. This is particularly the case insofar as the placebo group appeared to use more antihistamine than the SCG group. An alternative study designed to avoid this type of overlap would involve the concomitant use of only topical (nasal SCG and/or beclomethasone dipropionate) therapy of nasal symptoms.

There are no known side effects from ophthalmic SCG apart from stinging at the time of application. This effect was generally mild and was similar in the two groups, and it is therefore assumed that it was due to the preservative, benzalkonium chloride, or some other characteristic of the buffer rather than the SCG. The topical use of SCG in asthma and allergic rhinitis has been associated with remarkably few side effects apart from mild local irritation at the time of use and rare allergic reactions.¹⁶

The treatment of allergic conjunctivitis has previously been unsatisfactory. Vasoconstrictor and antihistamine eye drops are sometimes effective, but not invariably so. Adrenocortical steroid eye drops are associated with potentially serious side effects, including glaucoma and aggravation of herpetic keratitis. We consider that SCG ophthalmic solution is a useful addition to the treatment of allergic conjunctivitis.

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REFERENCES

1. Foreman, J. C., and Garland, L. G.: Cromoglycate and other antiallergic drugs: A possible mechanism of action, *Br. Med. J.* **1**:820, 1976.
2. Northern General Hospital, Brompton Hospital and Medical Research Council Collaborative Trial, *Br. Med. J.* **1**:361, 1976.
3. Hopper, I., and Dawson, J. P.: The effect of disodium cromoglycate in perennial rhinitis, *J. Laryngol. Otol.* **86**:725, 1972.
4. Holopainen, E., Backman, A., and Salo, O. P.: Effect of disodium cromoglycate on seasonal allergic rhinitis, *Lancet* **1**:55, 1971.
5. Frost, M.: Cromoglycate in aphthous stomatitis, *Lancet* **2**:389, 1973.
6. Heatly, E. V., Calcroft, B. J., Rhodes, J., Owen, E., and Evans, B. K.: Disodium cromoglycate in the treatment of chronic proctitis, *Gut* **16**:559, 1975.
7. Mani, V., Lloyd, G., Green, F. H. Y., Fox, H., and Turnberg, L. A.: Treatment of ulcerative colitis with oral disodium cromoglycate, *Lancet* **1**:439, 1976.
8. Chu, J., O'Connor, D. M., McElfesh, A. D., and Mueller, J.: Gastritis varioliformis, allergy and disodium cromoglycate, *Lancet* **1**:964, 1976.
9. Freier, S., and Berger, H.: Disodium cromoglycate in gastrointestinal protein intolerance, *Lancet* **1**:913, 1973.
10. Dolovich, J., Punthakee, N. D., MacMillan, A. B., and Osbaldeston, G. J.: Systemic mastocytosis: Control of lifelong diarrhea by ingested disodium cromoglycate, *Can. Med. Assoc. J.* **111**:684, 1974.
11. Easty, D. L., Rice, N. S. C., and Jones, B. R.: Clinical trial of topical disodium cromoglycate in vernal keratoconjunctivitis, *Clin. Allergy* **2**:99, 1972.
12. Rice, N. S. C., and Jones, B. R.: Vernal conjunctivitis, An allergic disease of the eyes of children, *Clin. Allergy*, **3**:629, 1973.
13. Kazdan, J. J., Crawford, J. S., Langer, H., and MacDonald, A. L.: Sodium cromoglycate (Intal) in the treatment of vernal keratoconjunctivitis and allergic conjunctivitis, *Can. J. Ophthalmol.* **11**:300, 1976.
14. Chatterjee, J., and Hargreave, F. E.: Atmospheric pollen and fungal spores in Hamilton, *Can. Med. Assoc. J.* **110**:659, 1974.
15. Ceska, M., Eriksson, R., and Varga, J. M.: Radioimmunosorbent assay of allergens, *J. ALLERGY CLIN. IMMUNOL.* **49**:1, 1972.
16. Sheffer, A. L., Ricklin, R. E., and Goetzl, G. J.: Immunologic components of hypersensitivity reactions to cromolyn sodium, *N. Engl. J. Med.* **293**:1220, 1975.