

Topical sodium cromoglycate (Opticrom®) relieves ongoing symptoms of allergic conjunctivitis within 2 minutes

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Twelve patients with seasonal allergic conjunctivitis caused by either birch or timothy grass pollen were challenged out of season in both eyes, with the relevant allergen. Itching, redness, swelling, and tearing were assessed on a 0–3 scale. When a positive reaction, i.e., at least 4 points, had occurred in both eyes, one drop of 2% sodium cromoglycate was administered to one eye and one drop of placebo to the other eye in each patient, in a double-blind, randomized fashion. Symptoms were then assessed after 2, 10, 30, and 60 min. Sodium cromoglycate was statistically better than placebo in reducing the symptoms at 2, 10, and 30 min after the treatment had been administered, showing that topical application of 2% sodium cromoglycate can quickly relieve ongoing symptoms of allergic inflammation in the eye.

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For more than 10 years, sodium cromoglycate, in the form of eye-drops (Opticrom®, Fisons plc), has been widely used as an antiallergic agent. Numerous studies have confirmed its efficacy and safety in relieving symptoms of seasonal allergic conjunctivitis (6, 8, 13), as well as chronic allergic conjunctivitis, e.g., vernal conjunctivitis (7). Sodium cromoglycate is thought to act chiefly through inhibition of mast-cell degranulation (15). Therefore, it is administered prophylactically to susceptible patients before the onset of the anticipated allergen exposure.

There is widespread belief that a course of treatment with ocular sodium cromoglycate over a period of days is needed to achieve symptom reduction, although it was recently shown in an open study that 2% sodium cromoglycate can reduce symptoms within 1 h (12). It is also our experience that patients are relieved within 1 h of treatment. We surveyed 79 patients who used sodium cromoglycate eye-drops, of whom 62 reported a therapeutic response within 30 min of the first dose. This finding encouraged us to conduct a placebo-controlled study to determine whether sodium cromoglycate is effective against ongoing allergic inflammation in the conjunctiva.

Material and methods

Twelve patients entered the study, all with a history of seasonal allergic conjunctivitis for at least the 2 previous years, caused by either birch ($n = 8$) or timothy ($n = 4$) pollen. The sensitization had been confirmed by a positive skin prick test (SPT) within the last 12 months. The age range was 18–41 years (mean 29 years). Four of the patients were men. Exclusion criteria were any ocular symptom during the last 48 h, any ocular treatment during the last month, and desensitization during the last year. None of the patients had been taking oral antihistamines, steroids, or nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 month of entering the study. The patients were all selected without any previous investigation of their responsiveness to sodium cromoglycate eye-drops.

A conjunctival provocation test with the relevant pollen extract (standard allergen purchased from ALK, Denmark) was performed outside the pollen season. The provocation procedure was started by giving the diluent of the allergen solution as a negative control. If no clinical reaction occurred, an allergen concentration of 1/10 of the dose giving a

Table 1. Scale for assessment of symptoms

Score	Patients' assessment		Doctor's assessment made with slit-lamp	
	Itching	Swelling	Redness	Tearing
0	No	No	No	Tear meniscus <0.3 mm
1	Mild	Folds around semilunar plica	Mild	Tear meniscus 0.3–0.5 mm
2	Moderate	Inferonasal limbal swelling	Moderate	Tear meniscus 0.5–0.7 mm
3	Severe	Total limbal swelling	Severe	Tear meniscus >0.7 mm

positive SPT was instilled. Each pair of eyes was identically challenged with dose increments of half-log steps (i.e., 1000, 3300, 10000 sq, etc.) every 10 min. Symptoms were assessed by slit-lamp examination 9 min after each challenge and graded on a 0–3 scale (Table 1). When a positive reaction, defined as a total symptom score of at least 4 in both eyes, appeared, one drop of 2% sodium cromoglycate was administered in one eye, and one drop of matching placebo in the other (i.e., subjects acted as their own control). The drops were administered by a nurse in a double-blind, randomized fashion. Both the active and the placebo eye-drops were unpreserved and taken from single dose units, being identical except for pH from the presence (pH 6.0) or absence (pH 5.3) of sodium cromoglycate. Post-treatment symptom assessments were performed at 2, 10, 30, and 60 min.

As a means of avoiding bias, the patients' and the doctor's score records were mutually blinded once the test treatment had been given. Furthermore, the patients were not allowed to look at their eyes in a mirror, or to rub their eyes.

The ratio between active and placebo at the different time intervals was tested with the two-tailed Student's *t*-test at the 95% confidence level ($\alpha = 0.05$). The protocol was approved by the ethics committee at the Karolinska Hospital (Stockholm, Sweden), and all the patients gave informed consent.

Results

The mean number of half-log steps needed to elicit a response as defined in the protocol was 4 (2–6) in birch-pollen-sensitive patients and 5 (3–7) in patients responsive to timothy pollen. The mean total symptom score (per eye) of the inflammatory response was 6 (5–9) and, at this point, only three patients had a score difference between the eyes (1, 1, and 2 points, respectively). Two of these patients received sodium cromoglycate in the eye with the higher initial total symptom score.

Conjunctivitis score ratios (i.e., mean total symptom scores at different post-treatment time points divided by mean total symptom scores at the time when medication was given) showed sodium cro-

moglycate to give a significantly greater reduction of symptoms than placebo after 2 min ($P < 0.01$), 10 min ($P < 0.05$), and 30 min ($P < 0.01$), with no significant difference in the score ratios after 60 min (Fig. 1).

Interocular (within-patient) score differences confirmed the better effect of the active treatment (Fig. 2).

Discussion

This is the first reported study showing the effect of a single drop of topical sodium cromoglycate in patients with ongoing conjunctivitis after allergen challenge. Although normally regarded as a prophylactic treatment for allergic diseases such as rhinoconjunctivitis and asthma, a recent study in asthmatic patients showed that sodium cromoglycate inhaled after allergen challenge delayed the late asthmatic response and prevented an associated increase in methacholine responsiveness (14). Can the observed action of sodium cromoglycate in our study be explained solely in terms of mast-cell-stabilizing activity? In the rat, 75% and 85% of all conjunctival mast cells showed some degree of degranulation

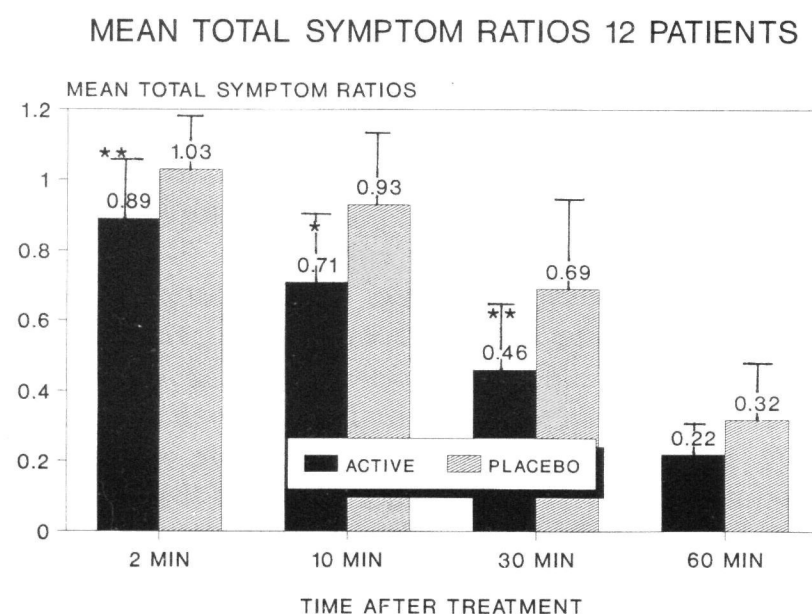


Fig. 1. Mean total symptom score ratio =

$$\frac{\text{Mean total symptom score time } x}{\text{Mean total symptom score time } 0}$$

T = SD. * $P < 0.05$; ** $P < 0.001$.

EFFECT OF TREATMENT

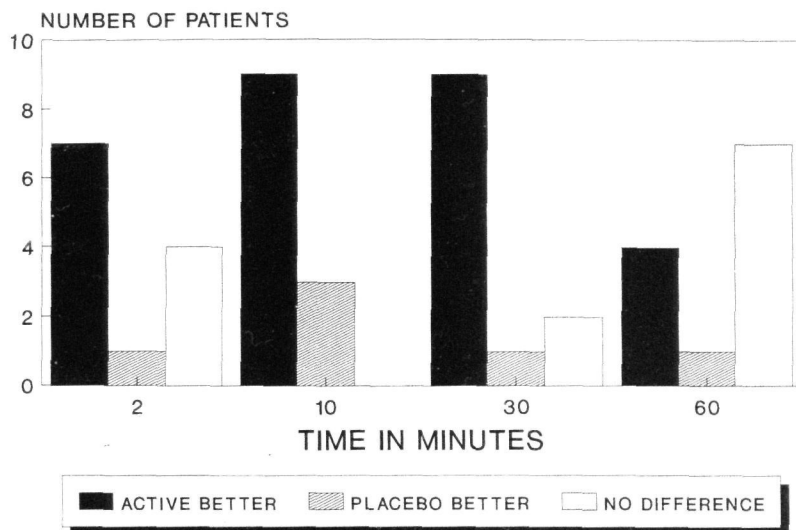


Fig. 2. Treatment efficacy expressed as score differences between eyes. For example, after 2 min, there were seven patients whose actively treated eye had lower score than placebo eye, one patient whose placebo eye had lower score, and four patients with no score difference between eyes.

30 min and 1 h, respectively, after ocular anaphylaxis (2). Tear histamine in man was increased 5 min after local allergen challenge and remained at high levels 20 min later (10). This suggests a sequential activation of different mast cells, as well as a successive degranulation in individual mast cells. Thus, there could be a benefit of a mast-cell-stabilizing agent even after the antigenic exposure. However, other data indicate that the vast majority of the involved mast cells degranulate early after the application of antigen. Tear histamine after local allergen challenge in guinea pig eyes peaked after 7 min, with a substantial decrease at 20 min (9). Furthermore, tryptase, which is liberated from released mast-cell granules, was significantly increased at 10 min but virtually normal at 40 min in tears after conjunctival provocation in man (3). In the present model, the resolution of the conjunctivitis symptoms in the untreated eyes 12–40 min after the final provocation also indicates an early interaction between allergen and the mast cells.

Could our results be due to an effect on other factors than mast-cell degranulation? An *in vitro* study of human lung mast cells has detected an inhibitory effect of sodium cromoglycate on the IgE-dependent release of prostaglandin (PG) D_2 , a membrane-synthesized mediator (4). PG D_2 is known to cause erythema and chemosis when applied to the human conjunctiva (1). Whether sodium cromoglycate can exert an effect on *de novo* synthesized membrane mediators regardless of previous triggering of the mast cells is not known. Mast-cell-unrelated inhibitory activities on afferent C-fibers (5) or on neutrophils (11) might also explain the acute effect of sodium cromoglycate in the allergic eye, but further

studies are needed to confirm that these findings are relevant for the eye.

In conclusion, we have shown the effectiveness of sodium cromoglycate 2% eye-drops on the ongoing allergic inflammation in the eye under experimental conditions. The results are not automatically applicable to a clinical setting. However, they agree with the findings in the previously conducted survey in which two-thirds of patients with pollen-caused conjunctivitis reported symptom relief within 30 min after one drop of sodium cromoglycate. Although our study was conducted under double-blind conditions with a placebo control, the ocular challenge model we used relies on a largely subjective scoring system (Table 1), as do most studies in this field. However, convenient objective measures with which to grade conjunctival inflammation are lacking today, and the development of such methods would improve future investigations of various therapeutic mechanisms in allergic conjunctivitis.

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