

# A double-blind group comparative study of ophthalmic sodium cromoglycate, 2% four times daily and 4% twice daily, in the treatment of seasonal allergic conjunctivitis

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In a multicenter, double-blind, single-dummy, group-comparative study, 169 patients received ophthalmic sodium cromoglycate 2% four times daily, and 170 patients received 4% ophthalmic sodium cromoglycate twice daily, together with placebo eye-drops twice daily, for the treatment of seasonal allergic conjunctivitis (SAC) to birch pollen. The treatment period was 4 weeks during the birch pollen season. Daily pollen counts were used to identify the peak 14-d period. Clinical examinations were made before the start of treatment, after 1 week of treatment, and at the end of the treatment period. Patients kept daily diary record cards of eye symptom severity and concomitant therapy. Symptoms were generally mild and, except for chemosis (week 4) and soreness (weeks 2 and 3), which were less in the 4% group ( $P \leq 0.05$ ), no significant treatment differences were seen for symptoms or for antihistamine rescue therapy. Both treatments were considered to be very or moderately effective by more than 90% of patients, and no treatment differences occurred in either clinicians' or patients' opinions of efficacy. The results indicate that the use of 4% sodium cromoglycate eye-drops twice daily is as effective and well tolerated as 2% sodium cromoglycate four times daily in the treatment of birch-pollen conjunctivitis.

M. Leino<sup>1</sup>, P. Montan<sup>2</sup>, F. Njå<sup>3</sup>

<sup>1</sup> Department of Ophthalmology, Kuopio University Hospital, Finland; <sup>2</sup> Saint Erik's Eye Hospital, Stockholm, Sweden; <sup>3</sup> Private Clinic for Paediatric Allergology, Høvik, Norway

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Markku Leino, MD  
Viljelijantie 4/6  
70260 Kuopio  
Finland

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Ophthalmic sodium cromoglycate (Lomudal®/Opticrom®, Fisons plc) is a well-established therapy in the treatment of a number of allergic eye disorders, including vernal keratoconjunctivitis (4, 5, 7, 11), giant papillary conjunctivitis (3, 13), and seasonal allergic conjunctivitis (SAC) (6, 10, 12). Other studies have confirmed that both 2% and 4% sodium cromoglycate treatments are effective in controlling SAC symptoms when administered four times daily (14, 19, 20). This efficacy is dose-related since 4% sodium cromoglycate proved to be significantly more effective than 2% in controlling the symptoms of SAC when administered four times daily (17). In addition, at least in the lung, the duration of action of topical sodium cromoglycate is related to dose (15, 16).

Sodium cromoglycate is a mast cell stabilizer which has a preventive, anti-inflammatory mode of

action. Thus, it blocks the release of histamine and other inflammatory mediators and has no intrinsic vasoconstrictor or antihistaminic activity (2, 18). Its efficacy is therefore dependent upon regular administration, implying a high degree of patient compliance. A number of studies have shown that compliance is not ensured even with drugs which give acute relief from painful and distressing symptoms (1, 8, 9). A simple, twice-daily treatment regimen, if efficacious, would be expected to lead to greater compliance and consequently a greater degree of symptom control.

The objective of this study was to compare the efficacy and tolerability of 4% sodium cromoglycate twice daily with 2% sodium cromoglycate four times daily in the treatment of SAC during the birch pollen season.

## Material and methods

A total of 339 patients with SAC caused by birch pollen entered the study at 13 centers: 10 in Sweden, two in Norway, and one in Finland. The initial visit was timed to take place about 1 week before the onset of the birch pollen season, just before the patients began to experience ocular symptoms. Birch pollen counts were recorded daily in the study areas and used both to predict the onset of symptoms and to identify the consecutive 14-d peak pollen challenge period for each center.

At the initial visit, patients were assessed for eligibility on the basis of a medical history of SAC, and positive RAST or skin prick tests (2+) to birch pollen within the last 12 months. Women who were pregnant or at risk of becoming pregnant were excluded from the study. Patients were also excluded if they had been treated with systemic or ocular corticosteroids or with high-dose (> 1000 µg daily) inhaled steroids during the last 3 months. Inhaled steroids up to 1000 µg and nasal steroids up to 400 µg daily were permitted, and also nasal sodium cromoglycate. Patients who exhibited perennial symptoms of allergic conjunctivitis, or who had taken ophthalmic sodium cromoglycate or oral antihistamines during the week preceding the study, were also excluded. All patients were allowed antihistamine plus vasoconstrictor (antazoline plus naphazoline) eye-drops for sole use as rescue medication if they became symptomatic in the week before the trial began. Once the study period had begun, the test treatment eye-drops were the only ocular therapy to be used, and each patient was then provided with 100 60-mg terfenadine tablets for use as concomitant rescue therapy.

At the start of the double-blind trial period, the eligible patients were randomly allocated to receive ophthalmic sodium cromoglycate, either 4% twice daily, or 2% four times daily, for 4 weeks. The single-dummy method was employed; that is, patients allocated to receive 4% sodium cromoglycate were treated with one drop per eye of the active medication (pack A) in the morning and in the evening, and one drop per eye of matching placebo (pack B), before lunch and before going to bed. The 2% group used one drop per eye of active treatment (pack A or B) each time. All treatments were presented as isotonic aqueous solutions, without benzalkonium chloride preservative, in unit dose packs of similar appearance, labeled A or B. Each unit dose pack was used for one dose (2 drops) only, and then discarded. The active solutions were made isotonic with either sodium chloride 0.82% (sodium cromoglycate 2% eye-drops) or glycerol 1.7% (sodium cromoglycate 4% eye-drops). The placebo eye-

drops contained glycerol 2.45% in isotonic aqueous solution.

At the first clinic visit of the trial period, the patients were given diary cards on which they recorded daily the severity of conjunctivitis symptoms, using a 0–4 scale. Daily use of test medication, terfenadine tablets, and any other medication was also recorded. Clinical assessments of redness, tearing, swelling of eyelids, and chemosis were made during the first visit at the start of the trial, after about 7 d of treatment, and at the end of the 4-week treatment period. At the second and third visits, both patient and investigator recorded their opinions of the test treatment.

Any comments relating to adverse or unusual symptoms were also recorded by the patients on the diary cards. At each visit, the investigator discussed with the patient any symptom which might have indicated an adverse drug reaction.

Patient compliance was monitored at the final visit by counting the number of unit dose vials and terfenadine tablets remaining.

The study was conducted in accordance with the principles of the revised Declaration of Helsinki (Hong Kong, 1989), and all patients or parents gave their informed consent.

### *Statistical analysis*

Diary cards, clinical assessments, and opinions of efficacy were analyzed by the nonparametric Wilcoxon rank sum test. Diary card data were analyzed by direct comparison between the two treatment groups. The peak pollen period was of primary interest, and patients withdrawing from the study were included in the efficacy analysis as long as they had taken their test treatment for at least half of this period. For completeness, a subsidiary analysis of diary card data for each week of treatment was also performed. Clinical assessment data were analyzed by comparing differences from admission at each subsequent visit.

As the treatment effect did not differ significantly between individual centers, combined results from all centers are presented. All statistical tests were two-sided and performed at the 5% level of significance.

## Results

### *Patient population*

A total of 339 patients (147 males and 192 females) aged 11–78 years took part in the study, of whom 169 were randomized to the 2% sodium cromoglycate group and 170 to the 4% sodium cromoglycate group. The mean age of the 2% group was 24.6 years (range 11–78 years), and that of the 4% group was

23.5 years (range 11–67 years) with a mean duration of disease of 9.8 and 10.7 years, respectively.

### Withdrawals

Nine patients withdrew from the study; four from the 2% group and five from the 4% group. Reasons for withdrawal were noncooperation/poor compliance (one (2%) and three (4%)), pregnancy (one (2%)), unrelated personal reason (one (2%)), and adverse reaction – swelling of eyelids (one (4%)), burning sensation (one (2%)). The ninth patient was retrospectively found to be ineligible as a result of taking systemic corticosteroids and was excluded from the analysis.

### Analysis of efficacy

**Diary card data.** Analysis of diary card data for the 14-d peak pollen period showed no significant treatment differences for individual symptoms or for total symptom score. Mean total symptom scores and pollen counts during the peak period are shown in Fig. 1. Analysis of weekly diary card data revealed low symptom scores during the first week, with mean values below 0.25 except for itching, which was 0.37 in the 2% group and 0.33 in the 4% group. Symptoms then showed some increase as the pollen season developed, but they were generally well controlled by both treatments, and mean scores remained below 1.0 (mild). The only statistically significant treatment difference ( $P < 0.05$ ) was for soreness/pain, in favor of twice-daily 4% sodium cromoglycate, after 2–3 weeks of treatment. No significant treatment differences were seen in total symptom scores for any 1-week period or during the peak pollen challenge (Table 1).

Antihistamine rescue therapy use increased slightly in both groups as the pollen season progressed, but overall use was low. From week 1 to week 4, the mean daily dose increased from 0.11 to 0.18 terfenadine tablets per d in the 2% group and from 0.10 to

Table 1. Effect of test treatments on total diary card symptom severity (sum of 0–4 scores (from none to very severe) for itching, redness, grittiness, tearing, and soreness/pain)

| Period      | Symptom score                     |        |                                   |        | Wilcoxon rank sum statistic | P value |
|-------------|-----------------------------------|--------|-----------------------------------|--------|-----------------------------|---------|
|             | Ophthalmic sodium cromoglycate 2% |        | Ophthalmic sodium cromoglycate 4% |        |                             |         |
|             | Mean                              | Median | Mean                              | Median |                             |         |
| Week 1      | 1.23                              | 0.57   | 1.09                              | 0.57   | 0.18                        | 0.86    |
| Week 2      | 1.38                              | 0.57   | 1.07                              | 0.43   | −1.08                       | 0.28    |
| Week 3      | 1.91                              | 1.14   | 1.43                              | 0.86   | −1.81                       | 0.07    |
| Week 4      | 1.95                              | 1.00   | 1.73                              | 1.07   | 0.00                        | 1.00    |
| Peak pollen | 2.01                              | 1.07   | 1.66                              | 1.00   | 0.62                        | 0.54    |

Treatment difference not significant ( $P > 0.05$ ).

0.22 tablets per d in the 4% group. No significant difference was seen between the treatment groups either for any week or for the 14-d peak period.

**Clinical assessments.** Clinical assessments after 1 and 4 weeks were compared with those at the start of trial treatment. Signs and symptoms were mild, and the only statistically significant treatment difference was for chemosis after 4 weeks, in favor of the 4% group ( $P = 0.05$ ). There were no significant treatment differences in either the patients' or clinicians' opinions of efficacy after 2 or 4 weeks of treatment. Over 60% rated treatment as "very effective", most of the remainder scoring "moderately effective" (Tables 2 and 3).

### Concomitant medication

Most of the patients took drugs to control rhinitis during the study, the most common being sodium cromoglycate (63 patients), budesonide (56), terbutaline (39), and flunisolide (34).

### Acceptability and safety

Four eye-related symptoms were recorded in the 2% group and 10 in the 4% group. Those recorded in the

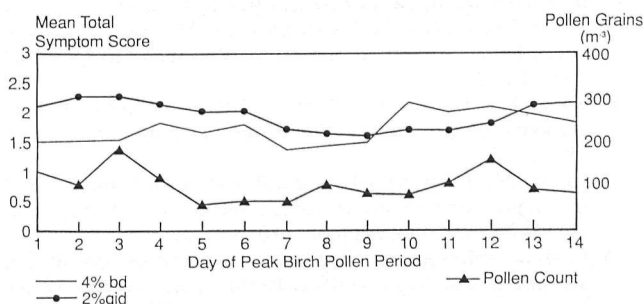


Fig. 1. Diary card total symptoms during course of 14-d peak birch pollen period in SAC patients treated with two dosage regimens of ophthalmic sodium cromoglycate.

Table 2. Clinicians' opinions of treatment efficacy

|                                                   | After 1 week |           | After 4 weeks |           |
|---------------------------------------------------|--------------|-----------|---------------|-----------|
|                                                   | 2% Group     | 4% Group  | 2% Group      | 4% Group  |
| Very effective                                    | 104 (62%)    | 110 (65%) | 104 (63%)     | 106 (64%) |
| Moderately effective                              | 51 (31%)     | 43 (26%)  | 51 (31%)      | 48 (29%)  |
| Slightly effective                                | 12 (7%)      | 15 (9%)   | 9 (5%)        | 10 (6%)   |
| Not effective                                     | 0 (0%)       | 0 (0%)    | 1 (1%)        | 1 (1%)    |
| Withdrawn/unknown                                 | 2            | 2         | 4             | 5         |
| Statistical significance (Wilcoxon rank sum test) | $P = 0.67$   |           | $P = 0.87$    |           |

Table 3. Patients' opinions of treatment efficacy

|                                                      | After 1 week |           | After 4 weeks |           |
|------------------------------------------------------|--------------|-----------|---------------|-----------|
|                                                      | 2% Group     | 4% Group  | 2% Group      | 4% Group  |
| Very effective                                       | 109 (65%)    | 116 (69%) | 108 (65%)     | 114 (69%) |
| Moderately effective                                 | 46 (28%)     | 44 (26%)  | 47 (28%)      | 47 (28%)  |
| Slightly effective                                   | 9 (5%)       | 7 (4%)    | 10 (6%)       | 3 (2%)    |
| Not effective                                        | 3 (2%)       | 0 (0%)    | 0 (0%)        | 1 (1%)    |
| Withdrawn/unknown                                    | 2            | 3         | 4             | 5         |
| Statistical significance<br>(Wilcoxon rank sum test) | P=0.34       |           | P=0.44        |           |

2% group were eye burning (2), other eye pain (1), and periorbital edema (1). Those in the 4% group were conjunctivitis (1), eye burning (2), eye dryness (1), eye itching (2), other eye pain (1), eye stinging (2), and periorbital edema (1). The most commonly reported non-eye-related symptom was headache (19 in the 2% group and 11 in the 4% group).

## Discussion

The primary objective of this study was to investigate whether a twice-daily dosing regimen with 4% sodium cromoglycate would be as effective against SAC as the well-established four-times-daily 2% regimen, because it can be assumed that twice-daily dosing would lead to better patient compliance. Overall, symptoms of SAC were mild and well controlled by both treatments, resulting in very few statistically significant treatment differences, none of which occurred during the important peak birch pollen period. The effectiveness of both treatments is reinforced by the very low mean usage of antihistamine rescue therapy (less than 0.2 terfenadine 60-mg tablets per day) and by the perceived efficacy, over 90% of patients in each group rating treatment as very or moderately effective.

One aspect of this treatment comparison requires further investigation, however. There is often a high placebo effect in ocular trials, particularly those involving extrinsic agents, and the washing action of the placebo solution may have beneficial effects. In our study, patients in both groups received eye-drops four times daily, whether active treatment or placebo dummy, and it is not possible to assess any effect which may have been due to the twice-daily placebo in the 4% sodium cromoglycate twice-daily group. This is a problem which cannot be overcome in a blind study, where the number of doses must remain constant across all groups. The inclusion of a four-times-daily placebo-treated group of patients might have increased the significance of the results but, while adding to the size and complexity of the trial, would still not have fully answered the question. In

addition, the presence of glycerol as a tonicity agent in the 4% formulation (and its placebo dummy) introduced another difference between the two treatments that could have had a bearing on the results.

Further work using an open study design for direct comparison between 2% sodium cromoglycate four times daily and 4% sodium cromoglycate twice daily would help to clarify the situation. Nevertheless, the results of our double-blind comparative study suggest that twice-daily treatment with the increased concentration of sodium cromoglycate should be equally efficacious in the management of SAC.

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