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Sodium cromoglycate eye drops: Regular versus “as needed” use in the treatment of seasonal allergic conjunctivitis

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Abstract

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Objective: The objective of this study was to compare the efficacy and side effects of sodium cromoglycate eye drops (Opticrom 2%) used regularly versus as needed in the treatment of seasonal (ragweed) allergic conjunctivitis.

Methods: A randomized, unblinded, parallel group comparison was performed during the 6 weeks of the ragweed pollen season. Sixty-two adults with ragweed pollen–induced conjunctivitis were recruited for the study from previous ragweed studies and notices in the local media. Two drops of

sodium cromoglycate were placed in each eye either four times daily (regular treatment group) or when needed, up to four times daily (prn group), from 1 week before and throughout the ragweed pollen season. Uncontrolled eye symptoms were treated with terfenadine 60 mg as needed, up to 120 mg daily. Subjects kept daily diaries for symptoms and medication requirements throughout the 6 weeks of treatment. The Rhinoconjunctivitis Quality of Life Questionnaire was administered and adverse experiences were reported after 1, 3, and 6 weeks of treatment.

Results: Diary eye symptoms were similar in the two treatment groups, but quality of life was better in the regular treatment group. There was a trend for the prn group to require more terfenadine for uncontrolled eye symptoms.

Conclusions: There may be some additional therapeutic benefit from using sodium cromoglycate eye drops regularly throughout the ragweed pollen season. (J ALLERGY CLIN IMMUNOL 1994;94:36-43.)

prn "As needed"

(Click on a term to search this journal for other articles containing that term.)

Key words: [Allergic conjunctivitis](#), [sodium cromoglycate](#), [quality of life](#)

Sodium cromoglycate eye drops (Opticrom 2% and 4%) have been shown, in several placebo-controlled clinical trials, to be effective in treating symptoms of allergic conjunctivitis.¹⁻⁶ In all of these trials, patients appear to have been experiencing symptoms at enrollment and showed progressive improvement over several days of treatment. In none of the studies were the eye drops used prophylactically to prevent the development of conjunctivitis. In keeping with the results of these studies, information included with the packaging of Opticrom eye drops indicates that improvement in symptoms of tearing, itching, and congestion can be expected within 10 days of commencing regular treatment. This may not be very encouraging for patients with troublesome conjunctivitis who are seeking quick relief.

In the immediate allergic reaction (type I), the union of antigen with reaginic antibody leads to the formation and release of the mediators of the local anaphylactic reaction. Sodium cromoglycate appears to block a step in the chain of events triggered by this union. In asthma pretreatment with sodium cromoglycate reduces the response of the airways to inhaled allergens.⁷ It is logical that sodium cromoglycate eye drops should also be most effective in treatment of conjunctivitis if they are started before patients come into contact with an allergen to which they are sensitive.

In this study we have compared prophylactic and regular use of sodium cromoglycate eye drops (2%) during the ragweed pollen season with the more conventional approach to treatment in which the eye drops are used only when needed.

It has often been assumed that if symptoms recorded in a diary show improvement, the patients must be feeling better and be able to function better in daily activities. This may not always be the case. There are also patients who report that they are feeling better as a result of treatment, but our symptom diaries fail to capture these changes. Until recently, assessment of quality of life has been

considered rather a “soft” outcome. It is no more subjective than patient symptom diaries, and recent developments in instrument methodology have allowed us to develop quality of life instruments that are scientifically sound and have strong measurement properties. In this study we have used the Rhinoconjunctivitis Quality of Life Questionnaire to evaluate the effect of the two trial regimens on the aspects of the disease that patients have told us are most important to them.

Methods

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Subjects

Sixty-two adults (age range, 16 to 70 years) were recruited from a group of patients who had participated in hay fever studies in previous years and from notices placed in the local media. All were required to give a history of conjunctivitis that either required treatment or was associated with moderate to severe untreated symptoms during the previous two ragweed pollen seasons. Participants were required to be sensitive to ragweed pollen extract as determined by skin prick test and to be prepared to stay in the ragweed pollen area throughout the pollen season. Potential subjects were excluded if they were more than mildly sensitive to *Alternaria tenuis* or *Cladosporium* species or if they had perennial conjunctivitis or other eye conditions. Pregnant and nursing mothers were excluded as were patients who had received orally or intravenously administered steroids within 1 month or astemizole within 3 months of enrollment or if they had received allergen injection therapy within the previous 12 months. Patients with other illnesses that might have an impact on quality of life were excluded. All participants signed an informed consent form that had been approved by the McMaster University Medical Centre, Research Committee.

Study design

The study was an unblinded, randomized comparison between two parallel treatment groups over a 6-week period. Subjects had duplicate skin prick tests with 10-fold serial dilutions of ragweed pollen extract (2.5 to 25,000 Noon units) (Bencard Allergy Services, Weston, Ontario, Canada) and single dilutions of *A. tenuis*, *Cladosporium* species, and grass pollen extract. Subjects who met the entry requirements were matched in pairs according to five criteria: (1) skin sensitivity to ragweed pollen extract, (2) severity of ragweed pollen–induced conjunctivitis the previous year, (3) skin sensitivity to fungal spores, (4) skin sensitivity to grass, and (5) gender.

One subject in each pair was randomly assigned to the regular treatment group. In this group subjects were instructed to start using the sodium cromoglycate eye drops on Monday August 10, which was 1 week before ragweed pollen was expected in the air. They were instructed to put 2 drops into each eye four times each day (daily dose = 12.8 mg sodium cromoglycate) until Monday September 21, the end of the ragweed pollen season.

The other subject in each pair was assigned to the “as needed” (prn) group. In this group subjects were instructed to use 2 drops of sodium cromoglycate in each eye, when needed, up to a maximum of four times per day (maximum daily dose = 12.8 mg). They were instructed to start using the eye drops as soon as symptoms became troublesome and to continue using them regularly until symptoms were controlled. They were told to stop using the eye drops when symptoms were controlled but to start again as soon as symptoms redeveloped. In both treatment groups if eye symptoms were inadequately controlled with the maximum daily dose (12.8 mg of

sodium cromoglycate), patients were instructed to use terfenadine (60 mg), when needed, up to 120 mg daily.

All patients were given aqueous beclomethasone dipropionate nasal spray (Beconase Aq.) for treatment of nasal symptoms. They were encouraged to use 2 puffs in each nostril twice each day from August 10 until September 21 and to increase the dose to 2 puffs four times per day whenever nasal symptoms were troublesome. If patients had shown in a previous study,^{8 9} that their ragweed pollen-induced nasal symptoms could be well controlled with an intensive prn regimen, they were allowed to use this approach for symptom control. The aim of the beclomethasone dipropionate treatment was to ensure that nasal symptoms were as well controlled as possible and did not interfere with the assessment of the eye symptoms. Patients were not allowed to use terfenadine for uncontrolled nasal symptoms because this would have affected the eye symptom assessment. Patients with asthma used salbutamol, 2 puffs when needed, up to four times per day. Patients who required regular daily administration of salbutamol were asked to use beclomethasone dipropionate inhaler (400 µg daily) or the dose of inhaled steroid prescribed by their practitioner. Patients were instructed not to use any hay fever medications other than those prescribed by the study.

Every morning and every evening from August 10 to September 21, patients completed a symptom diary. They recorded the severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) and duration (0 = none, 1 = a few short episodes, 2 = many episodes, 3 = continuous) of eye itching, eye soreness, eye watering, eye swelling, and overall nasal symptoms. Each evening they recorded the amount of eye drops, nasal spray, terfenadine, and any non-hay fever medications they had used in the previous 24 hours.

Patients attended the clinic after 1, 3, and 6 weeks of treatment. The visit after 3 weeks was at the height of the ragweed pollen season. At each visit, patients completed the Rhinoconjunctivitis

Quality of Life Questionnaire,¹⁰ reported any adverse experiences, and had their diaries checked for accuracy. The medication instructions were reviewed to ensure that all subjects were using their rhinoconjunctivitis medication correctly.

Daily pollen counts were not available throughout this study, but a decade of regular observations in the Hamilton area has demonstrated that the ragweed pollen season is consistent both in dates and severity.^{11 12} Ragweed first appears during the third week in August, reaches a peak during the last week in August and the first week in September, and becomes minimal by the third week in September.

Statistical analysis

Mean weekly scores for symptoms and medication use were calculated from daily diary scores for each subject. Differences between the two treatment groups for symptom scores, medication use, overall quality of life, and quality of life in each of the individual domains were examined with a repeated measures analysis of variance with all available data included (intention to treat). The factors were treatment, time, and treatment-time interaction. Differences were considered significant at *p* value of less than 0.05 (one-sided).

Sixty-two subjects were enrolled in the study, and 58 completed it and contributed complete data sets (■ Table I). One subject in the regular treatment group was withdrawn when an eye infection developed after 1 week of treatment. One subject in the prn group withdrew after an appendectomy at 5 weeks, and another withdrew for family reasons after 3 weeks of treatment. A third subject in the prn group had an upper respiratory infection and was unable to complete the final week of treatment. All data have been included in the analysis up to the time of withdrawal.

TABLE I. Patient characteristics

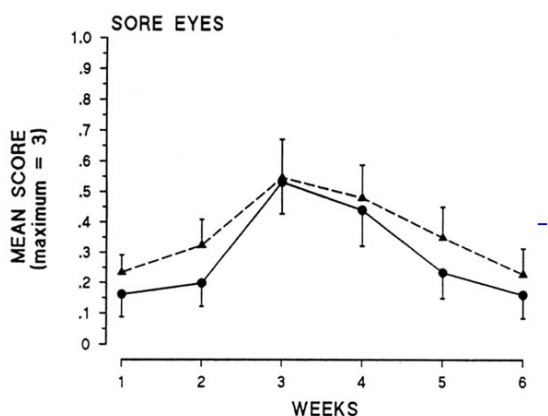
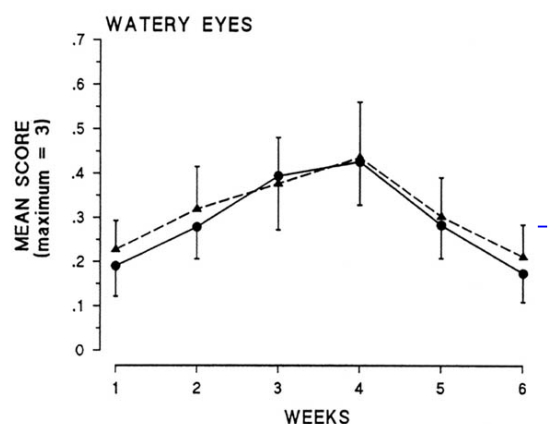
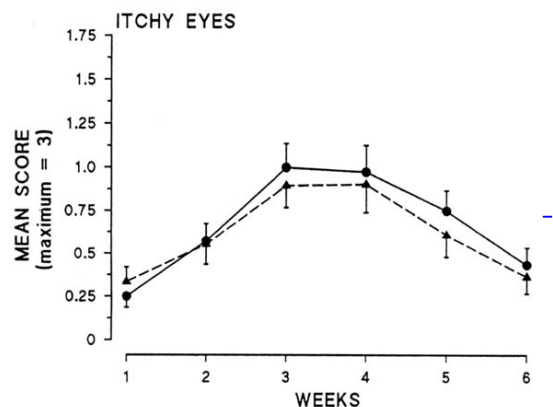
Characteristic	Regular treatment	PRN treatment
Number	31	31
Gender (M/F)	17/14	17/14
Mean age (yr) (SD)	42.9 (10.9)	42.4 (13.2)
Ragweed skin sensitivity (mean wheal diameter, mm) (SD)	3.83 (0.92)	3.94 (13.2)
Severity of ragweed-induced conjunctivitis the previous year*		
Mild	5	6
Mild/moderate	2	3
Moderate	9	10
Moderate/severe	10	7
Severe	5	5
No. of subjects sensitive to fungal spores	9	8
No. of subjects sensitive to grass pollen	30	29

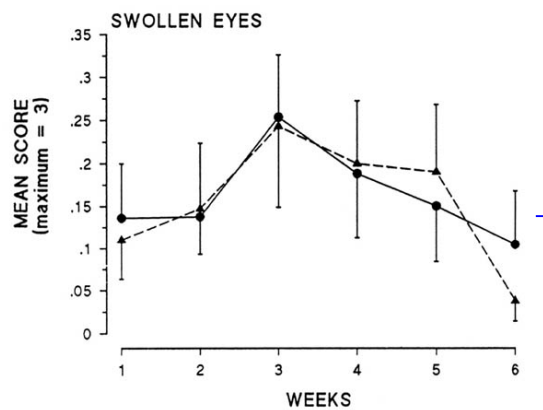
SD, Standard deviation.

*Estimated from medication requirements and symptom severity.

Over the 6 weeks of the study, there was no evidence of any difference in eye itchiness ($p = 0.28$), soreness ($p = 0.26$), wateriness ($p = 0.48$), or swelling ($p = 0.43$) between the two treatment groups (■ Fig. 1). However, there was a tendency for less terfenadine to be needed by the regular treatment group (■ Fig. 2), but the difference did not reach significance ($p = 0.09$).

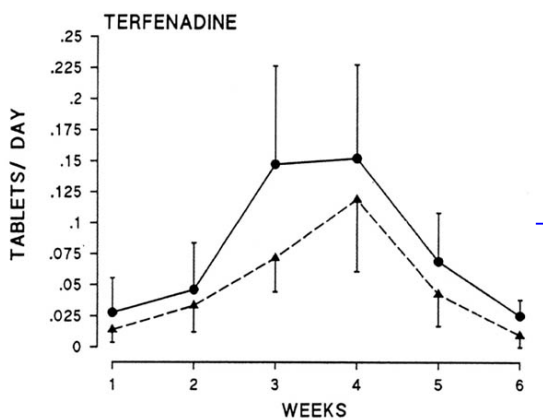
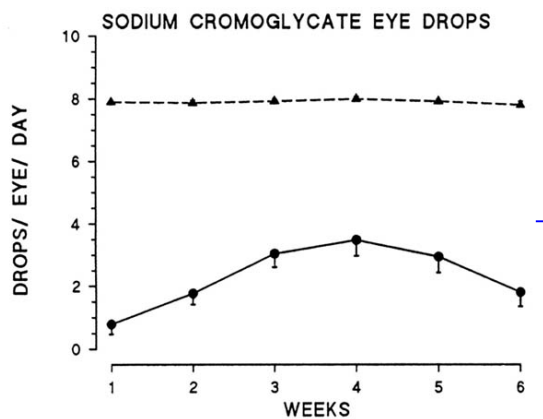
FIG. 1. Eye symptom scores from patient diaries. Circles represent the prn group, and triangles represent the regular treatment group. Error bars = standard error of the mean. Itchy eyes: $p = 0.28$, watery eyes: $p = 0.48$, sore eyes: $p = 0.26$, swollen eyes: $p = 0.43$.

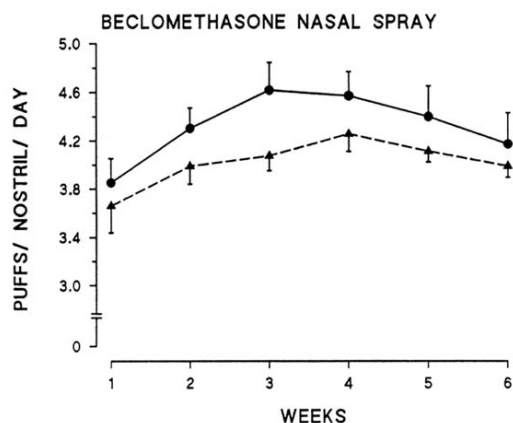
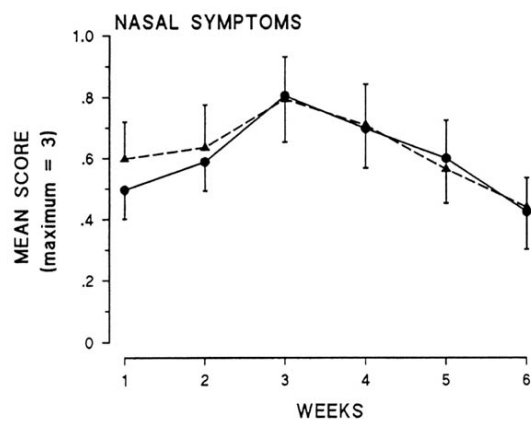




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FIG. 2. Medication use and nasal symptom scores from patient diaries. *Circles* represent the prn group, and *triangles* represent the regular treatment group. Error bars = standard of the mean. Eye drop use: $p < 0.0001$, terfenadine use: $p = 0.09$, nasal symptoms: $p = 0.49$, beclomethasone use: $p = 0.06$.

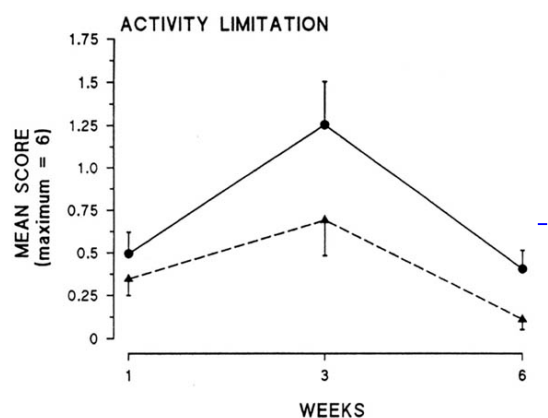
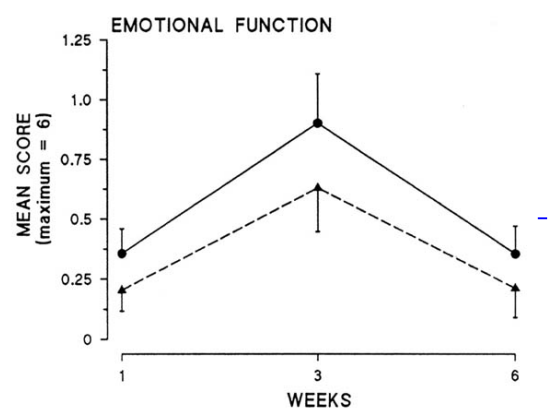
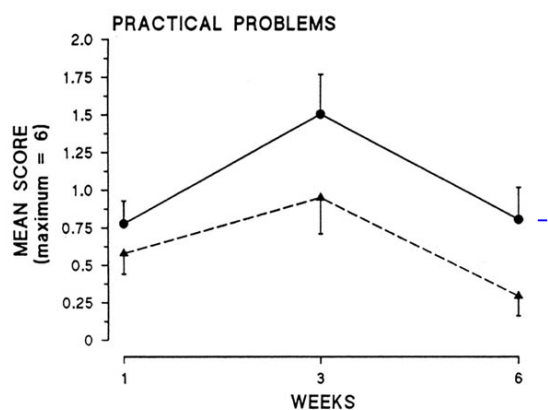
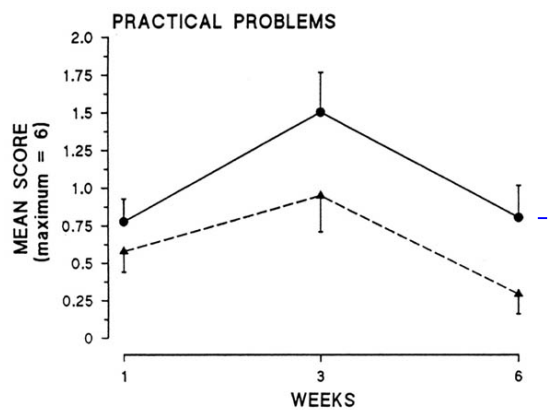


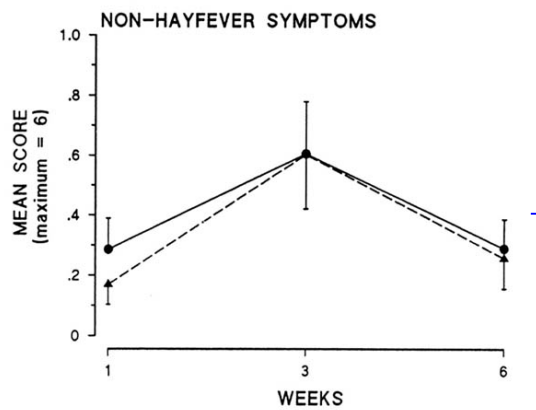


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When quality of life was compared after 1, 3, and 6 weeks of treatment, practical problems ($p = 0.03$) and activity limitations ($p = 0.03$) were significantly better in the regular treatment group (■ Fig. 3). At the height of the ragweed season, the difference in scores between the two groups was 1.27 for practical problems and 1.05 for activity limitation, where a change in score of more than 0.5 is considered to be a clinically important difference.¹³ A similar trend was seen for eye symptoms ($p = 0.23$), emotional function ($p = 0.11$), and overall quality of life ($p = 0.13$) (■ Figs. 3 and ■ 4). There was no evidence of any difference between the two groups for non-hay fever symptoms ($p = 0.32$) (■ Fig. 3). For sleep the trend favored the prn group, but again the difference was not significant ($p = 0.38$) (■ Fig. 4).

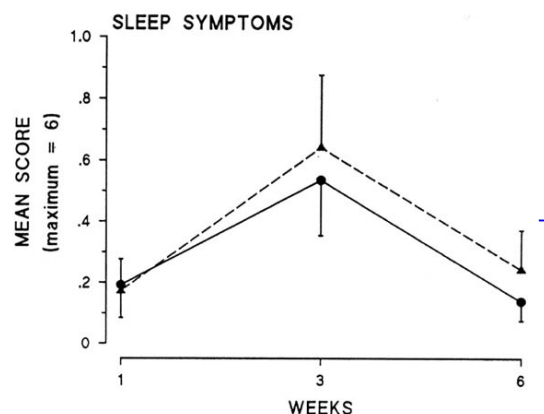
FIG. 3. Rhinoconjunctivitis Quality of Life. *Circles* represent the prn group, and *triangles* represent the regular treatment group. Error bars = standard error of the mean. Practical problems: $p = 0.03$, emotional function: $p = 0.11$, activity limitation: $p = 0.03$, non-hay fever symptoms: $p = 0.32$.

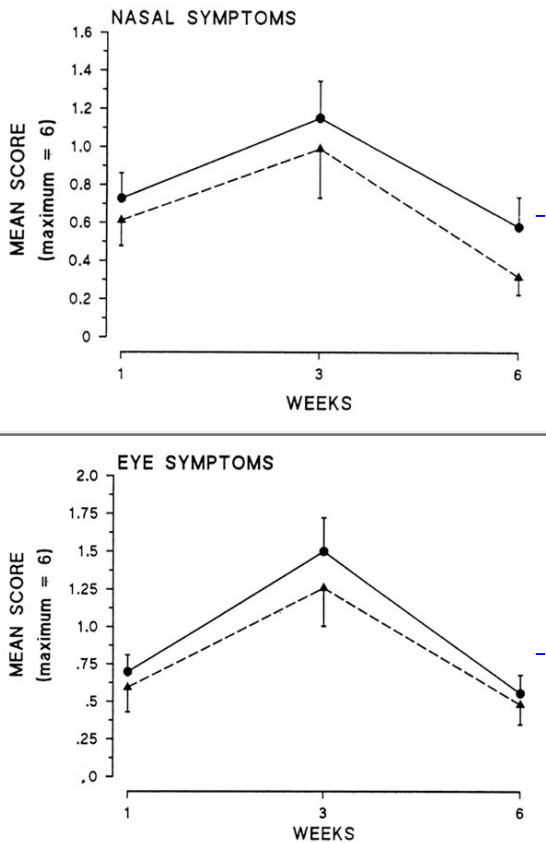




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FIG. 4. Rhinoconjunctivitis Quality of Life. *Circles* represent the prn group, and *triangles* represent the regular treatment group. Error bars = standard error of the mean. Overall quality of life: $p = 0.013$, sleep: $p = 0.38$, nasal symptoms: $p = 0.34$, eye symptoms: $p = 0.23$.





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Patients in the regular group used over three times as much sodium cromoglycate eye drops as those in the prn group ($p < 0.0001$) (■ Fig. 2). In the prn group the average daily use was 2.30 drops per eye per day, and in the regular treatment group, 7.90 drops per eye per day (expected amount = 8.0 drops per eye per day).

All adverse eye experiences reported by the patients are shown in ■ Table II. One patient in the regular treatment group was withdrawn after 1 week of treatment because of an eye infection. This was a problem that he had experienced in previous ragweed hay fever studies when using naphazoline hydrochloride eye drops. In this study the infection was not thought to be due to the sodium cromoglycate eye drops. He was treated by his ophthalmologist, and symptoms resolved. All other eye experiences were mild and not troublesome and were mainly related to some irritation on eye drop application. Other adverse experiences reported were headache, sore throat, nose bleed, dry mouth, thirst, insomnia, nausea, painful sinuses, and drowsiness. These were generally mild, transient, and equally distributed between the two treatment groups and did not necessitate withdrawal from the study.

TABLE II. Adverse eye experiences

Patient No.	Adverse experience
Regular group	
11	Temporary soreness and itching on application of eye drops.

- 20 Developed an eye infection after 1 week. Withdrawn from the study.
- 52 Temporary stinging on application of eye drops.
- 57 Painful eyes on second day of study. Lasted 1 day.

PRN group

- 7 Eye infection on the second day of the study (before using sodium cromoglycate eye drops). Treated with tobramycin. Resolved within 9 days.
- 13 Dry, itchy, sore eyes from Aug. 23 to Sept. 4.
- 50 Sept. 1 and 2, sore eye. Patient reported that the eye drops made her eyes too dry.
- 51 Occasional mild stinging on application of drops.

Throughout the study, beclomethasone dipropionate nasal spray use tended to be higher in the prn group than in the regular treatment group (mean difference = 0.30 puffs per nostril per day) ($p = 0.06$) (■ Fig. 2). However, there was no evidence of differences in scores between the two groups for both diary nasal symptoms ($p = 0.49$) (■ Fig. 2) and nasal symptom quality of life ($p = 0.34$) (■ Fig. 4).

Discussion

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The results of this study suggest that if sodium cromoglycate eye drops are started before allergic conjunctivitis symptoms develop and used regularly, they may be more effective in preventing a clinically relevant deterioration in some aspects of rhinoconjunctivitis quality of life during a pollen season than if the drops are only used when symptoms become troublesome.

When the two groups were compared for eye symptoms recorded in the daily diaries, the differences were not statistically significant. This raises the question: why were clinically important differences detected in some domains of the Rhinoconjunctivitis Quality of Life Questionnaire and not in diary-recorded eye symptoms? First, patients were instructed to use terfenadine whenever eye symptoms became troublesome, and there was a trend toward a greater need for terfenadine in the prn group. However, because only 18 of the 62 subjects required additional terfenadine, we may have failed to show a statistically significant difference because of insufficient power. Second, the quality of life questionnaire may be a more responsive instrument, and the conventional symptom diary may have failed to detect true treatment differences. Third, some of the benefits experienced as a result of using cromoglycate eye drops regularly may have an impact on a function important to the patient but not be captured by the conventional symptom diary.

It is unlikely that it was better control of the nasal symptoms and better ocular drainage that caused the improvement in the regular treatment group, because these subjects used less beclomethasone nasal spray and because there was no evidence of any difference in nasal symptoms between the two treatment groups both in the diaries and in quality of life. If beclomethasone nasal spray does by some means help eye symptoms, then because more nasal spray was used by the prn group, the observed difference between the two treatment groups may be an underestimate of true treatment difference. It is possible that the additional cromoglycate eye drops in the regular treatment group may have drained into the nose, and as a result, the regular eye drop users

needed less beclomethasone nasal spray to keep their nasal symptoms under control.

This study may have underestimated the real therapeutic difference between regular and prn use. The patients in the prn group were provided with hay fever medication and instructions before the pollen season, and they began using the eye drops as soon as symptoms started to develop. In real life, patients often wait for symptoms to become quite troublesome before seeking help, and there may be further delay in obtaining prescription medications. By this time, symptoms can be quite severe, and it may take several days to get them under control.^{1 6} Therefore the artificial environment of the clinical trial may have tended to overestimate the effectiveness of the prn regimen. In addition, we did not check compliance in the regular treatment group, and failure of patients to adhere to the treatment regimen of four times per day in the regular treatment group would mean that our observed difference between the two groups was an underestimate of the true treatment difference.

We have examined the effect of the intervention on four eye symptoms and seven domains of the questionnaire and in each case tested the null hypothesis of no difference between groups. There are a number of statistical strategies for dealing with the issue of multiple hypothesis testing on the same data set. One approach, dividing the p value by the number of tests (the Bonferroni adjustment), is excessively conservative when, as in our situation, outcomes are highly correlated with one another. Investigators can specify, before the study is undertaken, a single primary outcome on which the bottom line conclusions of the study will hinge. A third approach is to derive a single global test statistic, which in effect combines the multiple outcomes into a single measure. We have elected to simply present the results with uncorrected p values and allow the reader to determine the strength of inference that can be placed on the observations.

This was an unblinded study, and the differences observed between the two treatment groups could be explained by an expectation bias. We considered using a double-dummy technique to achieve blinding, but there are other biases associated with a blinded study in which one of the treatments is taken prn.⁸ In addition, most patients can only retain 2 drops in each eye at one time. When regular and prn beclomethasone dipropionate nasal spray use were compared in both a blinded⁹ and an unblinded study,⁸ the results were very similar.

To interpret the results of this study for clinical practice, it is important to take into consideration medication costs and patient willingness to take medications. Patients in the regular treatment group used approximately three times as much sodium cromoglycate as those in the prn group. Most patients are unwilling to take more medication than is necessary. Therefore the practical interpretation of this study is that some patients will be satisfied with the therapeutic benefit of prn use. However, clinicians should consider prophylactic, regular use of sodium cromoglycate eye drops in patients who experience inadequate control with prn use.

We thank the patients who participated in the study. We thank Glaxo Canada for providing Aq. Beconase, Ventolin, and Beclovent; Marion Merrell Dow Canada for providing Seldane; and Bencard Allergy Services for providing allergy skin test extracts. We also thank Ms. Lauren Griffith and Dr. Andrew Willan for statistical advice.

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Publishing and Reprint Information

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- *From ^athe Department of Clinical Epidemiology and Biostatistics and ^bthe Department of Medicine, McMaster University, Hamilton, Ontario, Canada.*
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Articles with References to this Article

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This article is referenced by these articles:

Allergic Rhinitis and Its Impact on Asthma

Journal of Allergy and Clinical Immunology, The
November 2001, part 2 • Volume 108 • Number 5

Jean Bousquet, MD, PhD, Paul van Cauwenberge, MD, PhD, Nikolai Khaltaev, MDIn collaboration with the World Health Organization

FULL TEXT

Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire

Journal of Allergy and Clinical Immunology, The
August 1999, part 1 • Volume 104 • Number 2

Elizabeth F. Juniper, MSc^a, Ann K. Thompson, MBA^b, Penelope J. Ferrie, BA^a, Jeremy N. Roberts, BSc^c

[ABSTRACT](#)

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