Brief Report

Comparison of Topical Nedocromil Sodium and Oral Terfenadine for the Treatment of Seasonal Allergic Conjunctivitis

Michael Alexander, MD,[1] Lawrence J. Rosen, MD,[2] and William H. Yang, MD[3]

Private practice, [1]Niagara Falls, [2]Downsview, and [3]Ottawa, Ontario, Canada

ABSTRACT

This double-masked, comparative, multicenter study was conducted to assess the onset of action and tolerability of nedocromil sodium 2% ophthalmic solution BID, 60-mg terfenadine tablets BID, and placebo in the treatment of seasonal allergic conjunctivitis. Two hundred sixty-eight patients in whom seasonal allergic conjunctivitis was diagnosed were assigned to 1 of 3 groups and administered study medication for 4 weeks. Patients' mean age was 33 years (range, 12 to 68 years); 57.8% (155 of 268) were female. Demographic characteristics were similar in all 3 groups. Although all 3 groups showed improvement in ocular symptoms, nedocromil sodium was associated with a statistically significantly faster onset of action than was terfenadine or placebo (P = 0.038). During the study, 29 nedocromil sodium–treated patients (36.7%) achieved control of symptoms in ≤2 minutes, and 61 (77.2%) achieved control in ≤15 minutes. The corresponding numbers were 21 (24.7%) and 50 (58.8%) in the terfenadine group and 25 (29.1%) and 48 (55.8%) in the placebo group. The frequency of adverse events was low and similar between groups (nedocromil sodium, 26; terfenadine, 32; placebo, 32). No severe treatment-related adverse events were reported. In conclusion, nedocromil sodium had a significantly faster onset of action than did terfenadine or placebo. ***Key words:*** nedocromil sodium, terfenadine, onset of action, seasonal allergic conjunctivitis.

INTRODUCTION

Seasonal allergic conjunctivitis is caused by an immediate-type hypersensitivity reaction in sensitized subjects after exposure to airborne allergens.[1] The interaction of the allergen with a specific antibody at-

Accepted for publication September 15, 1999.

0149-2918/99/$19.00

tached to conjunctival mast cells leads to the local release of vasoactive and inflammatory mediators (eg, histamine, leukotriene C_4, prostaglandin D_2).[2] These mediators cause the ocular allergic symptom complex of itching, watery discharge, redness, soreness, and photophobia.[1]

Drug therapy is intended to prevent the local allergic reaction. Treatments include topical instillation of sodium cromoglycate, which inhibits mediator release from conjunctival mast cells[3]; antihistamines, which block the effects of mediators postrelease; or, in more severe cases, corticosteroids.

Nedocromil sodium is the disodium salt of pyronoquinoline dicarboxylic acid and has topical antiallergic and anti-inflammatory activity.[4] It reduces the acute response to local antigen challenge by inhibiting the activation and release of biochemical mediators from conjunctival mast cells.[5]

In several placebo-controlled clinical studies,[6–9] nedocromil sodium was found to have a good safety profile and was effective and well tolerated in the treatment of allergic conjunctivitis. In studies during peak birch[6] or grass[7] pollen challenge, nedocromil sodium was significantly more effective than vehicle in reducing ocular symptoms ($P < 0.05$). It was significantly more effective than placebo in a pediatric population allergic to birch pollen ($P < 0.05$).[8] Nedocromil sodium was significantly more effective than vehicle in the treatment of symptoms of perennial allergic conjunctivitis not effectively controlled by sodium cromoglycate ($P < 0.05$).[9] Typically, vehicle-treated patients show some relief of conjunctival symptoms, an effect usually attributed to ocular irrigation. For example, in a comparison trial of nedocromil sodium and placebo, 36% of patients found placebo to be moderately or very effective, compared with 61% of patients who received nedocromil sodium.[10]

Terfenadine is a second-generation, orally active histamine$_1$ (H_1)-receptor antagonist that is highly selective for the H_1 receptor and has limited effect on the central nervous system.[11] Terfenadine blocks the H_1-receptor site for histamine after its release.[11] Unlike first-generation H_1-receptor antagonists, it has a low incidence of depressive effects on the central nervous system, with a sedative effect similar to that of placebo[11] and a duration of action that facilitates BID dosing.

We conducted a study to assess the onset of action and tolerability of nedocromil sodium administered BID with those of terfenadine administered BID in the treatment of ragweed pollen–induced conjunctivitis. To account for the irrigation effect and ensure proper masking, a topical placebo was included in the study design.

PATIENTS AND METHODS

Patients

Male or female patients ≥12 years of age were eligible to enter the study. Primary inclusion criteria were a diagnosis of seasonal allergic conjunctivitis, a positive skin-prick test to ragweed pollen (wheal ≥3 mm), and a history of requiring treatment for moderate to severe conjunctivitis after exposure to ragweed pollen.

Patients were not eligible for enrollment if they had concomitant ocular disease that could interfere with the action of the study medications; wore contact lenses; had significant systemic disease; were receiving immunotherapy for the first time or had received immunotherapy

followed by symptom resolution; were undergoing concurrent treatment with systemic corticosteroids, antihistamines, or other medications with systemic antihistamine effects; or were pregnant, at risk for pregnancy, or nursing.

All patients or their guardians provided written informed consent and were free to withdraw from the study at any time.

Study Design

We used a multicenter, double-masked, double-placebo comparative design. The study was conducted by 5 investigators at 4 centers in Canada during the 1989 ragweed pollen season (July through September). Patients were enrolled in the study within 2 weeks of the estimated onset of ragweed pollen season and began treatment with the study medications at the start of the season.

The study medications were nedocromil sodium 2% ophthalmic solution and 60-mg terfenadine tablets. The placebo agents (an inert ophthalmic solution and an inert tablet) were identical in appearance and content to the study medications minus the active ingredient, except that riboflavin was included as a colorant in the topical placebo to provide more effective masking.

Patients were randomly assigned to 1 of 3 groups. The study sponsor provided the random allocation code in sealed envelopes. All investigators and participants were masked to the code.

One group of patients received nedocromil sodium 2% ophthalmic solution and inert tablets, the second group received 60-mg terfenadine tablets and inert ophthalmic solution, and the third group received inert ophthalmic solution and inert tablets. All patients were instructed to administer 1 drop of the ophthalmic solution into each eye BID (morning and evening) and to take 1 tablet orally BID (morning and evening). The treatment was continuous over 4 weeks.

The only concomitant medications permitted were "artificial tear" eye drops and topical nasal medications. Patients were instructed to use this rescue medication only when absolutely necessary and to record such use in their study diaries.

Study visits were at entry (visit 1), start of treatment (visit 2), end of 2 weeks of treatment (visit 3), and end of 4 weeks of treatment (visit 4). Each study participant was given diary scorecards and instructed to rank symptom scores on a scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). The specific symptoms elicited were itching, soreness or gritty sensation, photophobia, watery discharge, and redness. Patients also recorded their use of study medication on the diary scorecards. Pollen counts were recorded using a rotorod sampler set at each study site for comparison with symptom severity. Rods were changed every 24 hours to obtain daily counts.

The study investigator assessed severity of itching, soreness or gritty sensation, photophobia, watery discharge, and redness at each study visit using the scale just described. At visits 3 and 4, patients were asked to rank their overall opinion of the masked study treatments using a scale of 0 (made worse), 1 (ineffective), 2 (slightly effective), 3 (moderately effective), and 4 (highly effective). At visit 4, patients were asked to rate the onset of action of the masked medications on a scale of 1 (≤2 minutes), 2 (2–15 minutes), 3 (15–30 minutes), 4 (30–60 minutes), 5 (1–2 hours), 6 (>2 hours), and 7 (not at all). At each visit, patients were asked to describe any adverse events that had occurred.

Statistical Analysis

Nonparametric methods were used to analyze the data. The Kruskal-Wallis test[12] was used to detect differences between the 3 groups. If a significant difference was found between groups for any variable, the Mann-Whitney *U* test[13] was used for pairwise comparisons to determine which pairs had statistically significant differences. The groups were compared for all centers using the Kruskal-Wallis test with adjustments for center (Mack-Skillings test).[12] All tests were 2-tailed, and significance was set at $P < 0.05$.

RESULTS

A total of 270 patients were enrolled in the study, and data from 268 were assessed. Two patients were excluded for noncompliance with the study protocol. There were 89 patients in the nedocromil sodium group, 89 in the terfenadine group, and 90 in the placebo group.

Patients' demographic characteristics are presented in Table I. There were more women (57.8%) than men (42.2%). The mean age was 33 years (range, 12–68 years). Seasonal allergic conjunctivitis had been diagnosed in all patients, and all patients had a positive skin test for ragweed pollen. There were no statistically significant differences between study groups in sex, age, number of years of symptoms, or time of year when symptoms peaked.

Twelve patients withdrew from the study: 5 (5.6%) in the nedocromil sodium group, 4 (4.5%) in the terfenadine group, and 3 (3.3%) in the placebo group. These patients were not included in the efficacy analyses at the end of the study. Lack of effect was cited by 4 patients receiving nedocromil sodium (4.5%), 2 patients receiving terfenadine (2.2%), and 2 patients receiving placebo (2.2%). One patient in each group (1.1%) withdrew because of a suspected adverse event. One patient in the terfenadine group (1.1%) left the study because of a severe concurrent infection not related to treatment. There were no significant differences between groups in terms of withdrawals.

The peak pollen period in 1989 was from August 23 through September 9 at all 4 centers. The mean pollen count was 307.7 grains/m^3 at centers 1 and 2, 54.5

Table I. Demographic characteristics (N = 268).

Variable	Treatment Group		
	Nedocromil Sodium (n = 89)	Terfenadine (n = 89)	Placebo (n = 90)
Sex, no. (%)			
Female	49 (55)	49 (55)	57 (63)
Male	40 (45)	40 (45)	33 (37)
Age (y)			
Mean	32.7	33.1	33.2
Range	14–65	13–67	12–68
Mean disease duration (y)	15.0	16.0	14.7
Peak symptom period	August–September	August–September	August–September

grains/m^3 at center 3, and 295.8 grains/m^3 at center 4. Because the centers were located in different environments, differences in pollen counts were expected.

Onset of Action

At the end of the study, patients were asked how quickly the test treatment controlled their ocular symptoms and for how long the morning dose protected against these symptoms. These data were compiled to determine onset and duration of relief.

Data were not available for 5 patients in the nedocromil sodium group and 1 patient in the placebo group. A total of 29 patients (36.7%) in the nedocromil sodium group experienced relief of symptoms in ≤2 minutes, compared with 21 (24.7%) in the terfenadine group and 25 (29.1%) in the placebo group. In addition, 61 patients (77.2%) in the nedocromil sodium group reported relief of symptoms in ≤15 minutes, compared with 50 (58.8%) in the terfenadine group and 48 (55.8%) in the placebo group. When the responses were compared, the nedocromil sodium group exhibited a statistically significant faster onset of action than the other 2 groups on a pairwise comparison ($P = 0.038$ between groups, Kruskal-Wallis test). The onset of action with terfenadine was similar to that seen with placebo ($P = 0.690$). The onsets of action for nedocromil sodium, terfenadine, and placebo are shown in Table II and the figure. At the end of the study, comparable numbers of physicians and patients in the 3 groups rated treatment as moderately or highly effective (nedocromil sodium, 60% of physicians, 60% of patients; terfenadine, 60%, 60%; and placebo, 58%, 61%). There was no significant difference in symptom relief between nedocromil sodium– and terfenadine-treated patients. In the nedocromil sodium group, 59% of patients rated the test medication as providing moderate or full control of symptoms, compared with 50% of patients in the terfenadine group and 53% of patients in the placebo group.

Table II. Onset of action of nedocromil sodium, terfenadine, and placebo (N = 250).

Time (Score)	Treatment Group (no., %)*		
	Nedocromil Sodium (n = 79)	Terfenadine (n = 85)	Placebo (n = 86)
≤2 minutes (1)	29 (36.7)†‡§	21 (24.7)†	25 (29.1)†
2–15 minutes (2)	32 (40.5)†‡§	29 (34.1)†	23 (26.7)†
15–30 minutes (3)	5 (6.3)	6 (7.6)	13 (15.1)
30 minutes to 1 hour (4)	2 (2.5)	8 (9.4)	4 (4.7)
1 to 2 hours (5)	0	0	0
>2 hours (6)	0	0	4 (4.7)
Not at all (7)	11 (13.9)	21 (24.7)	17 (19.8)
Mean score	2.4	3.2	3.1

*Data were not available for 5 patients in the nedocromil sodium group and 1 patient in the placebo group.
†$P = 0.038$ between the 3 groups (Kruskal-Wallis test).
‡$P = 0.014$ versus terfenadine.
§$P = 0.037$ versus placebo.

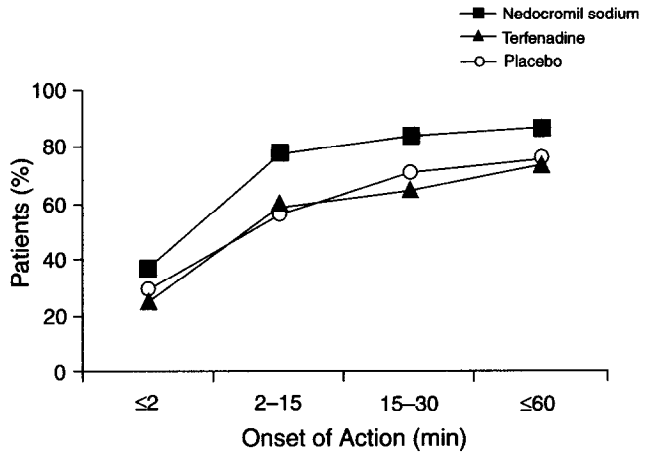

Figure. Onset of action of nedocromil sodium, terfenadine, and placebo. *P = 0.038 between the 3 groups (Kruskal-Wallis test). †P = 0.014 versus terfenadine. ‡P = 0.037 versus placebo.

Tolerability

When the 268 patients were asked to assess treatment as acceptable or not acceptable, 72 (81.0%) nedocromil sodium patients, 72 (81.0%) terfenadine patients, and 74 (82.0%) placebo recipients found the treatments acceptable. A total of 90 patients (26 nedocromil sodium, 32 terfenadine, 32 placebo) experienced adverse events during the study. The most common adverse event was headache (12 [13.5%] nedocromil sodium patients, 12 [13.5%] terfenadine patients, and 18 [20%] placebo recipients). The second most common symptom was local discomfort (stinging or burning sensation) after application of eye drops (6 [6.7%] nedocromil sodium patients, 1 [1.1%] terfenadine patient, and 4 [4.4%] placebo recipients).

DISCUSSION AND CONCLUSIONS

Our most important finding was that nedocromil sodium 2% ophthalmic solution had a statistically significant faster onset of action than did terfenadine tablets (P = 0.014) or placebo eye drops (P = 0.037). In fact, 36.7% of nedocromil sodium–treated patients reported relief of ocular allergy symptoms in ≤2 minutes, and 77.2% reported relief in ≤15 minutes. This speed of action is notable, especially when one considers that antihistamines can bind to histamine receptors and reduce symptoms quickly. Patients would be expected to prefer a faster-acting medication. Also, 86.1% of nedocromil sodium–treated patients reported feeling relief at some point, compared with 75.3% of terfenadine-treated patients.

Many agents used for treating seasonal allergic conjunctivitis (eg, H_1-receptor antagonists such as terfenadine, topical antihistamines, and mast-cell stabilizers) have a single mechanism of action. In contrast, nedocromil sodium appears to have a more comprehensive mechanism of action. It has been shown to inhibit the activation of mast cells, the release of pre-

formed and newly formed inflammatory mediators, and the activation of and mediator release from effector cells.[4,13,14] This apparent dual mechanism of action not only may be efficacious in patients who have never received medication for seasonal allergic conjunctivitis, but also may be valuable in patients whose condition is inadequately controlled with their current medication.

This study, conducted during the peak ragweed pollen season, demonstrated that all 3 groups had comparable improvements in all efficacy end points and that all treatments were well tolerated. However, nedocromil sodium had a statistically significant faster onset of action than did either terfenadine or placebo. This rapid onset of action, in addition to documented mast cell–stabilizing and anti-inflammatory effects, makes nedocromil sodium a valuable treatment option for seasonal allergic conjunctivitis.

ACKNOWLEDGMENT

This study was supported in part by Fisons Pharmaceuticals, Rochester, New York.

Address correspondence to: Michael Alexander, MD, 6453 Morrison Street, Suite 302, Niagara Falls, Ontario L2E 7H1, Canada.

REFERENCES

1. Allansmith MR, Ross RN. Ocular allergy. *Clin Allergy.* 1988;18:1–13.

2. Schleimer RP, Fox CC, Naclerio RM, et al. Role of human basophils and mast cells in the pathogenesis of allergic diseases. *J Allergy Clin Immunol.* 1985;76:369–374.

3. Allansmith MR, Ross RN. Ocular allergy and mast cell stabilizers. *Surv Ophthalmol.* 1986;30:229–244.

4. Gonzalez JP, Brogden RN. Nedocromil sodium: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and the therapeutic efficacy in the treatment of reversible obstructive airways disease. *Drugs.* 1987;34:560–577.

5. Corin R. Nedocromil sodium: A review of the evidence for a dual mechanism of action in the treatment of allergic conjunctivitis. *Clin Exp Allergy.* In press.

6. Leino M, Carlson C, Jaanio E, et al. Double-blind group comparative study of 2% nedocromil sodium eye drops with placebo eye drops in the treatment of seasonal allergic conjunctivitis. *Ann Allergy.* 1990;64:398–402.

7. Stockwell A, Easty DL. Group comparative trial of 2% nedocromil sodium with placebo in the treatment of seasonal allergic conjunctivitis. *Eur J Ophthalmol.* 1994;4:19–23.

8. Moller C, Berg IM, Berg T, et al. Nedocromil sodium 2% eye drops for twice-daily treatment of seasonal allergic conjunctivitis: A Swedish multicentre placebo-controlled study in children allergic to birch pollen. *Clin Exp Allergy.* 1994;24:884–887.

9. van Bijsterveld OP, Moons L, Verdonck M, Kempeneers HP. Nedocromil sodium treats symptoms of perennial allergic conjunctivitis not fully controlled by sodium cromoglycate. A double-masked, placebo-controlled group comparative study. *Ocul Immunol Inflamm.* 1994;2:177–186.

10. Melamed J, Schwartz RH, Hirsch SR, Cohen SH. Evaluation of nedocromil sodium 2% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. *Ann Allergy.* 1994;73:57–66.

11. Sorkin EM, Heel RC. Terfenadine: A review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 1985; 29:34–56.

12. Hays WL. *Statistics*. 4th ed. New York, NY: Holt, Rinehart and Winston; 1988.

13. Benbow AG, Eady R, Jackson D. The immunopharmacological actions of nedocromil sodium relative to the use of its 2% ophthalmic solution. *Eye*. 1993;7(Pt 3 Suppl):26–28.

14. Bissonnette EY, Enciso JA, Befus AD. Inhibition of tumour necrosis factor-alpha (TNF-α) release from mast cells by the anti-inflammatory drugs, sodium cromoglycate and nedocromil sodium. *Clin Exp Immunol*. 1995;102:78–84.