

# A Comparison of the Clinical Efficacy of Pheniramine Maleate/Naphazoline Hydrochloride Ophthalmic Solution and Olopatadine Hydrochloride Ophthalmic Solution in the Conjunctival Allergen Challenge Model

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## ABSTRACT

**Background:** The signs and symptoms of allergic conjunctivitis include ocular redness and itching. Two treatment options currently indicated for acute ocular allergic reaction are pheniramine maleate 0.3%/naphazoline hydrochloride 0.025% ophthalmic solution, an over-the-counter antihistamine/vasoconstrictor combination; and olopatadine hydrochloride 0.1% ophthalmic solution, a prescription antihistamine/mast cell stabilizer.

**Objective:** This study was designed to compare, at onset of action, the relative effectiveness of pheniramine/naphazoline and olopatadine, when administered before conjunctival allergen challenge (CAC), using the ocular allergy index (OAI) as the primary end point.

**Methods:** This was a prospective, randomized, double-masked, contralateral, active- and placebo-controlled, single-center study of the CAC model. The first 2 study visits established and confirmed the subjects' ocular allergic reaction (no medication administered). At visit 3, the subjects were randomly assigned to 1 of 3 contralateral (right eye vs left eye) treatment combinations: pheniramine/naphazoline + olopatadine, pheniramine/naphazoline + placebo, or olopatadine + placebo. Medication was given 10 minutes before CAC. The subjects' erythema in the ciliary, conjunctival, and episcleral vessel beds; eyelid swelling; chemosis; and itching were evaluated at 7, 12, and 20 minutes after CAC. The OAI was calculated as a composite score of 6 signs and symptoms of allergic conjunctivitis to assess global severity. Between-treatment differences in OAI scores were used to evaluate efficacy. Subjects were asked their eye drop preference at the conclusion of visit 3.

**Results:** Subjects (n = 83) ranged in age from 20 to 70 years (mean, 42.5 years), 61.4% (n = 51)

were female, and 94.0% (n = 78) were white. Both pheniramine/naphazoline and olopatadine were associated with significantly lower OAI scores than placebo at all 3 time points (all,  $P < 0.001$ ). OAI scores were significantly lower with pheniramine/naphazoline than with olopatadine at 12 and 20 minutes ( $P = 0.005$  and  $P = 0.001$ , respectively).

**Conclusion:** In this patient sample, studied in a CAC model of onset of action, prophylactic pheniramine/naphazoline was more effective than olopatadine and placebo in alleviating the signs and symptoms of the acute ocular allergic reaction, as measured by the OAI. (*Clin Ther.* 2005;27:568–577) Copyright © 2005 Excerpta Medica, Inc.

**Key words:** eye allergy, conjunctival allergen challenge, Visine-A, Patanol.

## INTRODUCTION

The signs and symptoms of allergic conjunctivitis are caused by environmental allergens that, in sensitized individuals, induce the degranulation of mast cells in the conjunctiva and the release of numerous proinflammatory and proallergy mediators. Among these allergic mediators is histamine, which induces itching by binding to histamine<sub>1</sub> (H<sub>1</sub>) receptors. Histamine and other vasoactive allergic mediators contribute to the ocular redness, chemosis, tearing, and eyelid swelling of allergy by increasing capillary permeability and vasodi-

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lation.<sup>1,2</sup> In the ocular allergic reaction, the sign and symptom most prevalent and bothersome to patients are redness (ie, vasodilation) and itching, respectively.

Some estimates indicate that up to 30% of the general population experiences the signs and symptoms of allergic conjunctivitis,<sup>3</sup> and this number is increasing.<sup>4,5</sup> With a greater number of allergy patients in the general population, the use of antiallergy medications is also rising, and a broad spectrum of pharmaceutical agents is now available to treat each patient's specific signs and symptoms. Clinical trials are important for evaluating the comparative merits of this broad treatment selection, and the conjunctival allergen challenge (CAC) model provides a well-controlled environment for comparing ocular allergy treatments.

The CAC model has been developed as a standardized means of inducing the allergic reaction in a reproducible manner for the conduct of clinical trials. The CAC model has been used extensively in pivotal Phase III programs and in Phase IV studies to assess the efficacy of ocular antiallergic agents.<sup>6-12</sup> Skin test results are used to determine the allergen to which a patient has the greatest sensitivity, and conjunctival challenge is then performed using specific, serially diluted allergens to determine the degree of reactivity in the eye. CAC studies typically use a 3-visit design: determination of allergen type and dose at the first visit, confirmation of reactivity at the second visit, and testing of the efficacy of antiallergic agents at subsequent visits.<sup>6</sup> A CAC study can assess efficacy at the onset of action by using a relatively short time interval between medication dosing and challenge (eg, 10 minutes). The CAC model can also be used to assess duration of action by lengthening this interval to several hours (eg, 4, 8, or 12 hours).<sup>7-12</sup>

In this study, the CAC model was used to evaluate 2 topical ophthalmic antiallergic agents at onset of action: olopatadine hydrochloride 0.1% ophthalmic solution\* (olopatadine) and pheniramine maleate 0.3%/naphazoline hydrochloride 0.025% ophthalmic solution† (pheniramine/naphazoline). Olopatadine is a dual-action antihistamine and mast cell stabilizer that has a rapid onset of action and a duration of action of ~8 hours.<sup>13</sup> Olopatadine exerts its effects by specific H<sub>1</sub> receptor antagonism and mast cell stabilization, inhibiting the release

of many of the mediators involved in the allergic reaction. Pheniramine/naphazoline is a combination of an antihistamine and an alpha-adrenergic agonist vasoconstrictor. The onset of action is rapid, with efficacy occurring within ~3 minutes; however, the labeled dosing regimen of up to 4 times per day implies a considerably shorter duration of action than olopatadine.

Pheniramine/naphazoline was originally a prescription medication (previously named AK-Con-A®) that was approved by the Food and Drug Administration (FDA) for sale over the counter (OTC) in 1996 in the United States under the brand name OcuHist. Pheniramine/naphazoline is indicated for the temporary relief of itchy, red eyes due to pollen, ragweed, grass, animal hair, and dander.<sup>14,15</sup> Olopatadine was approved by the FDA in 1996 and is available by prescription in the United States and in Japan, Australia, and several countries in Europe and South America. In the United States, olopatadine is indicated for treatment of the signs and symptoms of allergic conjunctivitis.<sup>15,16</sup>

The objective of this study was to compare, at onset of action, the relative effectiveness of these 2 FDA-approved and marketed ophthalmic antiallergic products, when administered before CAC, using the ocular allergy index (OAI) as the primary end point. The OAI compiles validated standard components of the ocular allergic reaction in a manner similar to the composite scores used in clinical evaluations of the total nasal allergic reaction.<sup>17-19</sup>

## SUBJECTS AND METHODS

### Subjects

Eligible subjects were aged ≥18 years, were able to follow the instructions of the study, and agreed to avoid disallowed medications (including systemic or topical antihistamines, mast cell stabilizers, and corticosteroids) during the required washout periods and throughout the study. Subjects were also required to have a positive skin test within 2 years to confirm their reactivity to allergen(s), a positive history of allergic conjunctivitis, and no active ocular allergic reaction at the time of the study. Patients were excluded if they had any ocular or systemic condition that the investigator believed would endanger them or inhibit their ability to participate in the study.

This study was a prospective, randomized, double-masked, contralateral (right eye vs left eye), active- and placebo-controlled, single-center CAC study in which medication was administered before challenge. The

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†Trademark: Visine-A® (Pfizer Consumer Healthcare, Pfizer Inc., Morris Plains, New Jersey).

protocol and informed consent were reviewed and approved by an ethical review board (IntegReview, Inc., Austin, Texas), and written informed consent was obtained from all subjects.

### Ocular Allergy Index

The primary end point used in this study was the OAI,<sup>17-19</sup> which summarizes the signs and symptoms of ocular allergy into one global rating. The OAI comprises the scores for erythema in the ciliary, conjunctival, and episcleral blood vessel beds; chemosis; eyelid swelling; and itching. The signs and symptoms included in the OAI were also evaluated individually. Each sign and symptom was rated on a standardized grading scale of 0 to 4 points (0 = none; 4 = extremely severe), with half-point ratings allowed, with the exception of eyelid swelling, which was rated on a scale of 0 to 3 points (0 = none; 3 = severe), with no half-point ratings allowed. Thus, the possible scores for the OAI ranged from 0 to 23.

Each component included in the OAI has been used in CAC studies and has been well validated in the past. This study is the first instance in which the OAI has been used. The OAI is not a questionnaire or measurement instrument that itself is used to gather patient data, but is simply a means of compiling those data by summing the individual (previously validated) symptom or sign scores into a global score.

### Study Visits

The study design included 3 visits. At visit 1, we recorded the subjects' demographic data, medical history, medication history, and visual acuity according to criteria of the Early Treatment Diabetic Retinopathy Study.<sup>20</sup> A urine pregnancy test was administered for all women of childbearing potential. Any woman who had a positive pregnancy test or refused to use a reliable contraceptive throughout the study was excluded from participation. A biomicroscopic examination with a slit lamp was performed to establish a baseline, to exclude any patients with an active ocular allergic reaction (defined as redness at score  $>1$  in any of the 3 vessel beds and any itching), and to identify any ocular conditions that, in the investigator's opinion, would affect the subject's ability to participate. Bilateral CAC was then performed on qualified subjects by administration of increasing doses of allergen to which each individual had sensitivity. Dosing was performed at 10-minute intervals until a positive reaction occurred. A positive

reaction was defined as  $\geq 2$  redness in  $\geq 1$  of the 3 vessel beds and  $\geq 2$  itching in both eyes. If a subject did not attain a positive qualifying reaction, he or she was excluded from further participation.

The purpose of visit 2 was to confirm the allergen type and dose at which each subject qualified. The ocular allergic reaction was confirmed by CAC with the single qualifying dose used at visit 1. At visit 2, at 7, 12, and 20 minutes after CAC, subjects graded itching and eyelid swelling, and the investigator graded redness in the 3 vessel beds (ciliary, conjunctival, and episcleral) and chemosis. A positive reaction was defined as redness score  $\geq 2$  in  $\geq 1$  of the 3 vessel beds and itching score  $\geq 2$  in both eyes, plus an OAI score  $\geq 8$ . Any subject not achieving a positive reaction was excluded from further participation. This visit confirmed patient reactivity and consistency of sign and symptom severity, as measured on standardized scales, with exposure to a set level of allergen.

At visit 3, qualifying subjects were randomly assigned to 1 of 3 treatment combinations, in which 1 of the 2 study eye drops was instilled in 1 eye and the other eye drop was instilled in the contralateral eye (before challenge): pheniramine/naphazoline + olopatadine, pheniramine/naphazoline + placebo, or olopatadine + placebo. These 3 treatment combinations were administered according to computer-generated random assignment to 1 of 6 different sequences (Table I).

The study medication was instilled in a double-masked fashion in equal quantities (40  $\mu$ L via calibrated pipette) into each eye according to the previously established randomization scheme. Ten minutes after medication instillation, CAC was performed, and signs and symptoms were evaluated (as specified at visit 2) at 7, 12, and 20 minutes after CAC. In addition, ~25 minutes after CAC, the subjects were asked a forced-choice question regarding which eye drop they preferred in terms of overall efficacy. Any adverse events were recorded, and subjects exited the study.

At each of the 3 visits, the subjects could receive an eye drop of a currently marketed, topical OTC ophthalmic antiallergic agent (other than the test agent, pheniramine/naphazoline) immediately before departure from the office to alleviate any discomfort caused by the allergic reaction.

### Statistical Analysis

Power calculations were made on the basis of estimates of the performance of the 2 agents from the lit-

Table I. Treatment sequences by antiallergy agent and eye.

| Sequence | Right Eye               | Left Eye                 |
|----------|-------------------------|--------------------------|
| 1        | Olopatadine*            | Pheniramine/naphazoline† |
|          | Pheniramine/naphazoline | Olopatadine              |
| 2        | Olopatadine             | Placebo                  |
|          | Placebo                 | Olopatadine              |
| 3        | Pheniramine/naphazoline | Placebo                  |
|          | Placebo                 | Pheniramine/naphazoline  |

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erature on this CAC model. With 40 patients in the pheniramine/naphazoline + olopatadine treatment combination, the study had >90% power to detect a difference in OAI means of 2.08 (eg, the difference between a mean of 2.17 for pheniramine/naphazoline and a mean of 4.25 for olopatadine), assuming that the common SD was 2.3, using a pairwise Student *t* test with a 2-sided significance level of 0.05.

The statistical analysis for efficacy was based on intent-to-treat subjects, and the analysis for safety was based on all enrolled subjects. Between-treatment comparisons for OAI and each of its components were performed with a pairwise Student *t* test from an analysis of covariance model, with treatment as a fixed effect, subject as a random effect, and the corresponding baseline as a covariate. Treatment-by-baseline interaction was also examined.

Between-treatment differences in OAI were evaluated for clinical and statistical significance for each of the treatment combinations. Clinical significance for OAI scores was defined as  $\geq 1$  unit difference, and statistical significance for the OAI and for individual signs and symptom scores was defined as  $P < 0.05$ .

Forced-choice query analysis consisted of a sign test on preference within the pheniramine/naphazoline + olopatadine treatment combination and a chi-square analysis of the proportion of patients in each placebo eye drop combination who preferred the active treatment administered to the contralateral eye.

## RESULTS

Eighty-three subjects completed the study, ranging in age from 20 to 70 years (mean, 42.5 years). Fifty-one subjects (61.4%) were female; 78 (94.0%) were white, 1 (1.2%) was black, and 4 (4.8%) were Hispanic. Iris

colors were brown (55.4% [ $n = 46$ ]), blue (21.7% [ $n = 18$ ]), hazel (12.0% [ $n = 10$ ]), and green (10.8% [ $n = 9$ ]). No significant differences were found in any demographic parameters or in any allergic assessments, including OAI scores, at baseline among the 3 treatment-combination groups.

At visit 3, the evaluation visit, the OAI score was calculated as the sum of redness in 3 vessel beds (ciliary, conjunctival, and episcleral), itching, chemosis, and eyelid swelling. OAI scores were comparable at baseline for all 3 groups (pheniramine/naphazoline, olopatadine, and placebo). Ten minutes after pretreatment with study medication, CAC was performed. Both pheniramine/naphazoline and olopatadine were associated with significantly lower OAI scores than placebo at all time points ( $P < 0.001$ ). OAI scores were significantly lower with pheniramine/naphazoline than with olopatadine at 12 minutes and 20 minutes ( $P = 0.005$  and  $P = 0.001$ , respectively; Table II; Figure 1).

Individual signs and symptoms (Table II; Figures 2 to 7) were also recorded and analyzed. Eyes treated with either pheniramine/naphazoline or olopatadine had significantly lower signs and symptom scores than placebo in all assessments (ie, redness in 3 vessel beds, itching, eyelid swelling, and chemosis) at all time points. Compared with olopatadine, pheniramine/naphazoline was associated with significantly lower ciliary vessel redness (at 12 and 20 minutes;  $P = 0.014$  and  $P = 0.002$ , respectively), conjunctival vessel redness (7, 12, and 20 minutes;  $P = 0.001$ ,  $P < 0.001$ , and  $P < 0.001$ , respectively), and episcleral vessel redness (7, 12, and 20 minutes; all,  $P < 0.001$ ), as well as lower chemosis scores (12 and 20 minutes;  $P = 0.011$  and  $P = 0.009$ , respectively). Olopatadine was associated

Table II. Differences in adjusted mean ocular allergy index scores\* between baseline and treatment visit 3 by antiallergy treatment.

| Parameter                   | Time After CAC, min | Pheniramine/Naphazoline <sup>†</sup> vs Placebo |        | Olopatadine <sup>‡</sup> vs Placebo |        | Pheniramine/Naphazoline vs Olopatadine |        |
|-----------------------------|---------------------|-------------------------------------------------|--------|-------------------------------------|--------|----------------------------------------|--------|
|                             |                     | Difference, Unit (%)                            | P      | Difference, Unit (%)                | P      | Difference, Unit (%)                   | P      |
| Itching                     | 7                   | -1.39 (-60.3)                                   | <0.001 | -1.69 (-73.4)                       | <0.001 | 0.30 (49.3)                            | 0.029  |
|                             | 12                  | -1.29 (-63.2)                                   | <0.001 | -1.45 (-71.5)                       | <0.001 | 0.17 (28.9)                            | 0.186  |
|                             | 20                  | -1.08 (-70.4)                                   | <0.001 | -1.17 (-76.1)                       | <0.001 | 0.09 (23.9)                            | 0.437  |
| Ciliary vessel redness      | 7                   | -1.27 (-68.4)                                   | <0.001 | -1.06 (-57.2)                       | <0.001 | -0.21 (-26.3)                          | 0.061  |
|                             | 12                  | -1.25 (-60.8)                                   | <0.001 | -0.96 (-46.9)                       | <0.001 | -0.29 (-26.2)                          | 0.014  |
|                             | 20                  | -1.19 (-59.4)                                   | <0.001 | -0.80 (-40.1)                       | <0.001 | -0.39 (-32.2)                          | 0.002  |
| Conjunctival vessel redness | 7                   | -1.21 (-62.5)                                   | <0.001 | -0.85 (-43.9)                       | <0.001 | -0.36 (-33.1)                          | 0.001  |
|                             | 12                  | -1.19 (-55.8)                                   | <0.001 | -0.74 (-34.7)                       | <0.001 | -0.45 (-32.3)                          | <0.001 |
|                             | 20                  | -1.14 (-55.5)                                   | <0.001 | -0.67 (-32.5)                       | <0.001 | -0.47 (-34.1)                          | <0.001 |
| Episcleral vessel redness   | 7                   | -1.37 (-68.5)                                   | <0.001 | -0.94 (-47.0)                       | <0.001 | -0.43 (-40.7)                          | <0.001 |
|                             | 12                  | -1.25 (-56.2)                                   | <0.001 | -0.82 (-37.1)                       | <0.001 | -0.42 (-30.4)                          | <0.001 |
|                             | 20                  | -1.20 (-56.8)                                   | <0.001 | -0.69 (-32.6)                       | <0.001 | -0.51 (-35.9)                          | <0.001 |
| Chemosis                    | 7                   | -0.63 (-71.1) <sup>‡</sup>                      | <0.001 | -0.48 (-54.6)                       | <0.001 | -0.15 (-36.4)                          | 0.065  |
|                             | 12                  | -0.73 (-66.7)                                   | <0.001 | -0.52 (-47.5)                       | <0.001 | -0.21 (-36.6)                          | 0.011  |
|                             | 20                  | -0.72 (-64.3)                                   | <0.001 | -0.48 (-43.1)                       | <0.001 | -0.24 (-37.2)                          | 0.009  |
| Eyelid swelling             | 7                   | -0.47 (-71.5)                                   | <0.001 | -0.49 (-73.6)                       | <0.001 | 0.01 (7.8)                             | 0.838  |
|                             | 12                  | -0.53 (-72.9)                                   | <0.001 | -0.44 (-59.7)                       | <0.001 | -0.10 (-32.9)                          | 0.243  |
|                             | 20                  | -0.51 (-70.0)                                   | <0.001 | -0.42 (-57.6)                       | <0.001 | -0.09 (-29.4)                          | 0.274  |
| Ocular allergy index        | 7                   | -6.40 (-66.1)                                   | <0.001 | -5.59 (-57.7)                       | <0.001 | -0.81 (-19.8)                          | 0.057  |
|                             | 12                  | -6.31 (-61.1)                                   | <0.001 | -5.03 (-48.7)                       | <0.001 | -1.28 (-24.2)                          | 0.005  |
|                             | 20                  | -5.91 (-61.5)                                   | <0.001 | -4.31 (-44.8)                       | <0.001 | -1.60 (-30.1)                          | 0.001  |

CAC = conjunctival allergen challenge.

\*Each sign and symptom was rated on a standardized grading scale of 0 to 4 points (0 = none; 4 = extremely severe), with half-point ratings allowed, with the exception of eyelid swelling, which was rated on a scale of 0 to 3 points (0 = none; 3 = severe), with no half-point ratings allowed. Thus, the possible scores for the ocular allergy index ranged from 0 to 23.

<sup>†</sup>Trademark: Visine-A® (Pfizer Consumer Healthcare, Pfizer Inc., Morris Plains, New Jersey).

<sup>‡</sup>Trademark: Patanol® (Alcon Laboratories, Inc., Fort Worth, Texas).

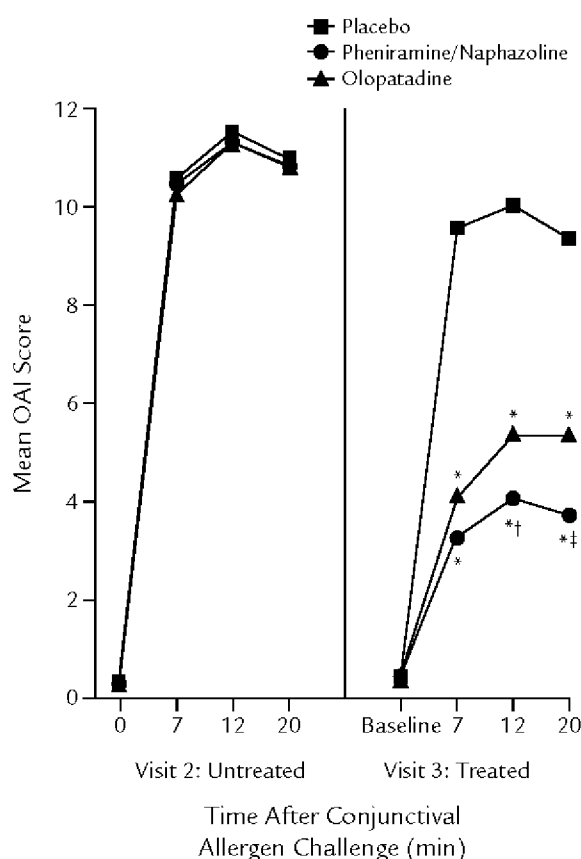


Figure 1. Primary efficacy variable: ocular allergy index (OAI), 0 to 23 scale. \* $P < 0.001$  versus placebo; † $P = 0.005$  versus olopatadine; ‡ $P = 0.001$  versus olopatadine.

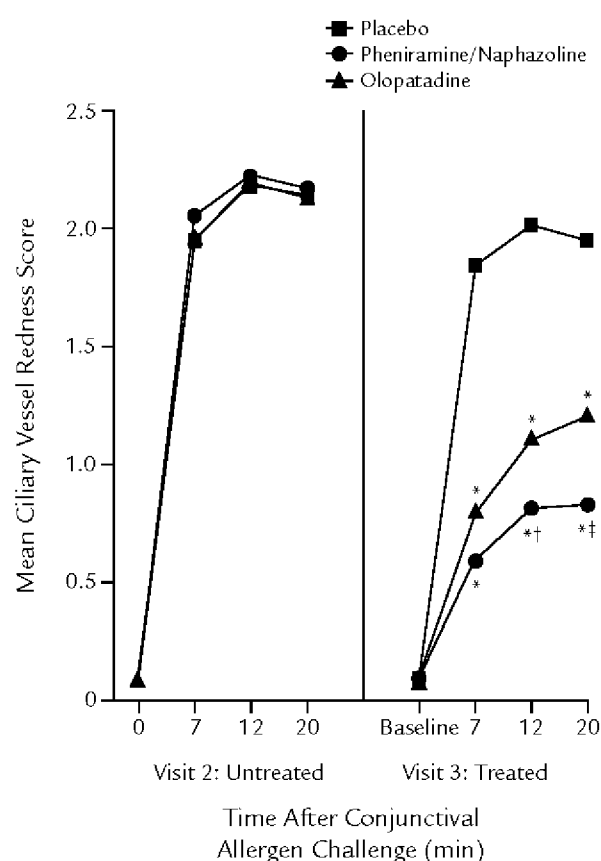


Figure 2. Secondary efficacy variable: ciliary vessel redness, 0 (none) to 4 (extremely severe) scale. \* $P < 0.001$  versus placebo; † $P = 0.014$  versus olopatadine; ‡ $P = 0.002$  versus olopatadine.

with significantly lower itching as compared with pheniramine/naphazoline at 7 minutes ( $P = 0.029$ ); no other statistically significant differences were present.

Results of the forced-choice query showed that all subjects who had received active treatment in 1 eye (olopatadine or pheniramine/naphazoline) and placebo in the contralateral eye preferred the active treatment. For subjects receiving pheniramine/naphazoline in one eye and olopatadine in the contralateral eye, 24 (57.1%) preferred pheniramine/naphazoline; the remaining 18 subjects (42.9%) preferred olopatadine. The preference was not significantly different from parity ( $P = \text{NS}$ ). It should be noted that this study was not powered to detect a preference difference. A much larger sample size would be necessary to achieve statistical significance for the preference results observed in this study.

Three adverse events occurred in the study: 1 headache, 1 foreign-body sensation in both eyes, and 1 ear infection. Each of these occurred and abated before randomization and instillation of the study medications. No serious adverse events were recorded.

## DISCUSSION

The results of this study show the antiallergic effectiveness of both pheniramine/naphazoline and olopatadine in the prevention of an acute ocular allergic reaction. Both medications demonstrated significantly greater inhibition of the ocular allergic reaction than placebo at all time points (all,  $P < 0.001$ ).

For this study, we sought a single measure that indicated overall efficacy and therefore used the OAI. Although the OAI score is not a traditional validated

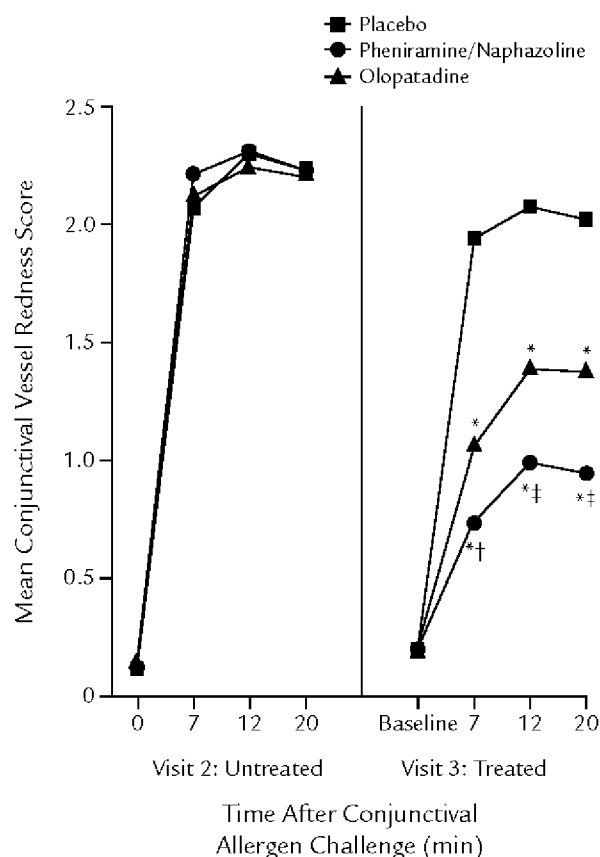


Figure 3. Secondary efficacy variable: conjunctival vessel redness, 0 (none) to 4 (extremely severe) scale. \* $P < 0.001$  versus placebo; † $P = 0.001$  versus olopatadine; ‡ $P < 0.001$  versus olopatadine.

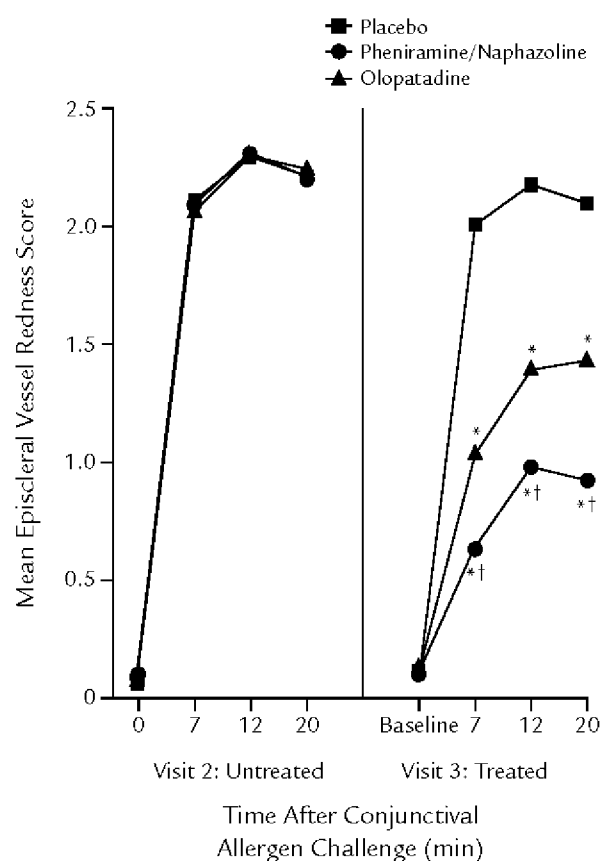


Figure 4. Secondary efficacy variable: episcleral vessel redness, 0 (none) to 4 (extremely severe) scale. \* $P < 0.001$  versus placebo; † $P < 0.001$  versus olopatadine.

measure used in studies of allergic conjunctivitis, its use is similar to that of the total nasal symptom score, a benchmark end point in clinical trials of nasal allergy,<sup>17-19</sup> including those submitted in support of new drug applications to the FDA. We used the OAI score to measure a constellation of ocular allergic signs and symptoms, which together provided a measure of overall efficacy against the acute ocular allergic reaction. We observed that pheniramine/naphazoline was associated with lower OAI scores than olopatadine at all time points and that these differences were statistically and clinically significant at 12 and 20 minutes ( $P = 0.005$  [1.28 unit difference] and  $P = 0.001$  [1.60 unit difference], respectively).

When asked to choose, 57.1% of subjects preferred pheniramine/naphazoline to olopatadine. However, this

was not found to be statistically significant, due to the size of the study. A much larger patient sample would be required to establish whether a statistically significant difference was present.

This study was designed to compare the therapies, with challenge 10 minutes after medication instillation, against the acute ocular allergic reaction. In individual sign and symptom evaluations, the data indicated that pheniramine/naphazoline was significantly better than olopatadine in conjunctival and episcleral redness (all time points), ciliary redness (at 12 and 20 minutes), and chemosis (at 12 and 20 minutes). Olopatadine-treated eyes had less acute itching than pheniramine/naphazoline at 7 minutes (Table II). No other statistically significant differences were noted. The significant differences in redness and chemosis favoring

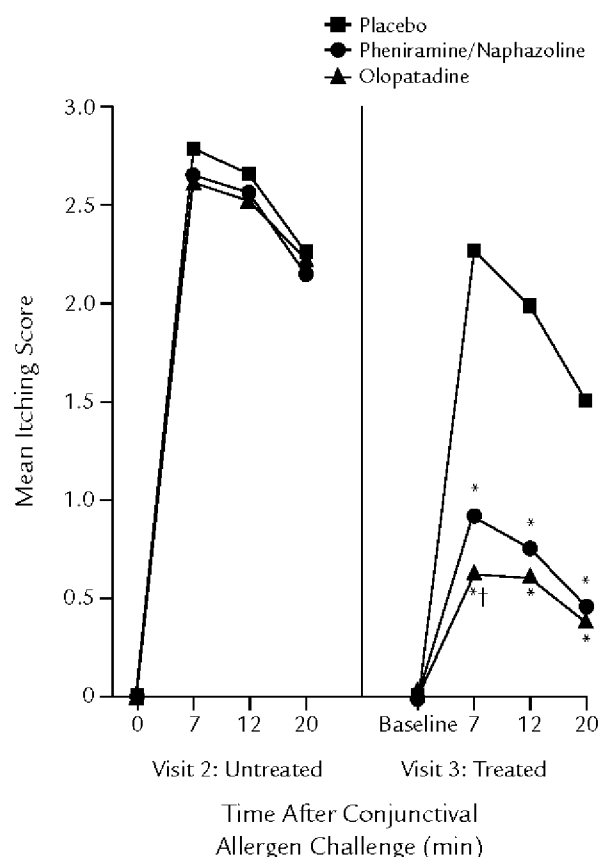


Figure 5. Secondary efficacy variable: ocular itching, 0 (none) to 4 (extremely severe) scale. \* $P < 0.001$  versus placebo; † $P = 0.029$  versus pheniramine/naphazoline.

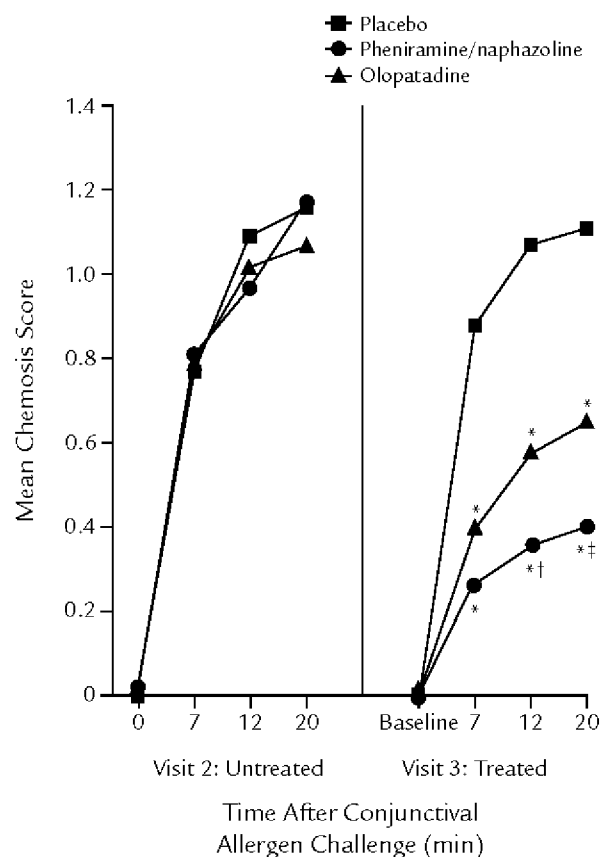


Figure 6. Secondary efficacy variable: chemosis, 0 (none) to 4 (extremely severe) scale. \* $P < 0.001$  versus placebo; † $P = 0.011$  versus olopatadine; ‡ $P = 0.009$  versus olopatadine.

pheniramine/naphazoline observed at 12 and 20 minutes (Table II) may be explained by the difference in time course for itching (which peaks at ~7 minutes after challenge) as compared with redness and chemosis (which peak later).<sup>21</sup> Thus, the greatest differences in treatment effect are discernible at the time points at which symptoms are typically the most severe.

Many options are available for the topical ophthalmic treatment of allergic conjunctivitis: tear substitutes for diluting and washing away allergen, H<sub>1</sub> antihistamine-vasoconstrictor combinations for mild allergic conjunctivitis, mast cell stabilizers for more chronic and cellularly mediated disorders, mild topical steroids for cases unresponsive to other therapeutic modalities, and agents with combined antihistaminic and mast cell stabilizing properties and

long duration of action, as well as several other options, including cyclosporine. The selection of first-line therapy therefore depends on several factors, including the severity of the allergic condition, the duration of discrete exposures to allergens, and length of the allergen season (ie, spring, fall, or perennial).<sup>22</sup>

This study did not include subjects with severe, continuous allergy and did not evaluate duration of action; all of the evaluation time points were within 30 minutes of study medication instillation. Thus, the results indicate that at onset, pheniramine/naphazoline can provide effective prophylaxis for mild to moderate, acute intermittent signs and symptoms of allergic conjunctivitis.

Other differences exist between the study agents. Pheniramine/naphazoline is an OTC product that is directly and easily available to consumers. Olopatadine

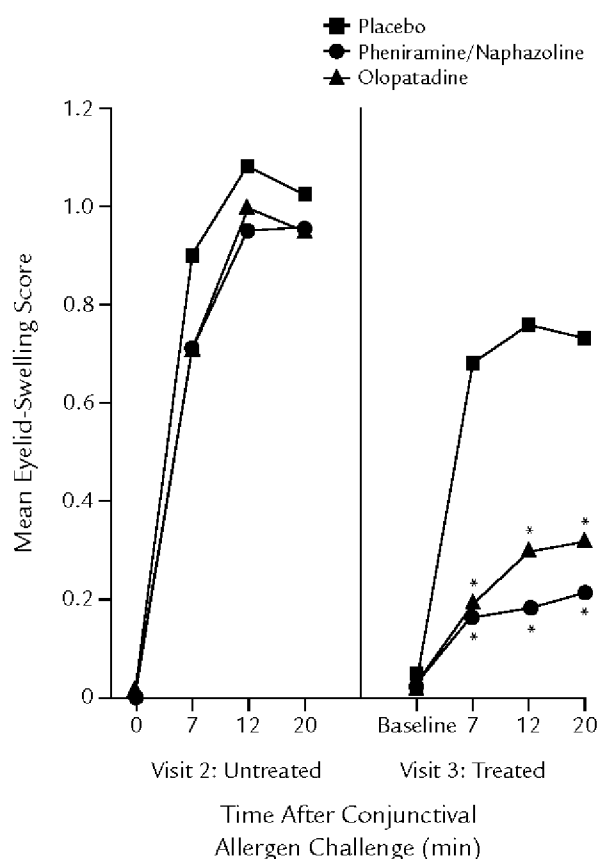


Figure 7. Secondary efficacy variable: eyelid swelling, 0 (none) to 3 (severe) scale. \* $P < 0.001$  versus placebo.

dine is available by prescription, which requires a visit to medical practitioners and pharmacies to obtain the medication. The 2 medications also have different frequencies of dosing. Olopatadine, with its longer duration of action, is indicated for use twice a day, whereas pheniramine/naphazoline, with its shorter duration, is indicated for use up to 4 times a day.

## CONCLUSIONS

In this patient sample, studied in a CAC model of onset of action, prophylactic pheniramine/naphazoline and olopatadine were more effective than placebo, and prophylactic pheniramine/naphazoline was more effective than olopatadine and placebo for alleviating the signs and symptoms of the acute ocular allergic reaction, as measured by the OAI. Pheniramine/naphazoline was an effective treatment for the signs

and symptoms of patients with short-duration, mild to moderate, intermittent ocular allergy in this CAC model study.

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