Efficacy and Response with Olopatadine Versus Epinastine in Ocular Allergic Symptoms: A Post Hoc Analysis of Data from a Conjunctival Allergen Challenge Study

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ABSTRACT

Objectives: This post hoc analysis used data from a previous study to more precisely evaluate the efficacy of olopatadine hydrochloride and epinastine hydrochloride in alleviating various levels of severity of ocular itching and conjunctival redness and to determine whether there were any significant differences in the number of responders to treatment.

Methods: The original study was a randomized, double-masked allergen challenge comparison assessment. Adult patients with allergic conjunctivitis were screened (visits 1 and 2); those who exhibited positive allergic reactions at both visits were randomized to 1 of 3 groups: olopatadine/epinastine, olopatadine/placebo, or epinastine/placebo. At visit 3, each eye was treated with study medication, and then challenged with allergen. Itching, redness, and chemosis assessments were recorded. For the present post hoc analysis, each eye in the olopatadine/epinastine group was separately classified at each time point, based on the pretreatment severity of their symptom (itching) and sign (conjunctival redness) scores, as moderate, moderate/severe, or severe. Data were analyzed to determine responders (eyes with itching and/or conjunctival redness scores of 0 [none]).

Results: Of 96 patients screened, 66 were randomized to treatment (36 women, 30 men; mean age, 44.38 years [range, 20–71 years]). Olopatadine-treated eyes exhibited lower mean itching scores than epinastine-treated eyes in the moderate/severe and severe groups at all 3 time points (3, 5, and 7 minutes), with significance in the moderate/severe group at 5 minutes ($P = 0.05$) and in the severe group at 5 and 7 minutes ($P = 0.017$ and $P = 0.02$, respectively). Olopatadine-treated eyes had mean conjunctival redness scores similar to epinastine-treated eyes in all severity groups at all time points (10, 15, and 20 minutes) except in the severe group at 10 minutes ($P = 0.03$). On response analysis, for itching, the proportion of responders was significantly greater in the olopatadine group versus the epinastine group 7 minutes after challenge (27 [50.9%] vs 14 [26.4%]; $P = 0.016$). For conjunctival redness, the proportion of responders was significantly greater with olopatadine treatment versus epinastine treatment at 15 and 20 minutes after challenge (15 minutes, 12 [22.6%] vs 1 [1.9%] [$P = 0.002$]; 20 minutes, 10 [18.9%] vs 1 [1.9%] [$P = 0.008$]).

An initial analysis of these data was previously published in Lanier R, Finegold I, D'Arienzo P, et al. Clinical efficacy of olopatadine vs epinastine ophthalmic solution in the conjunctival allergen challenge model. *Curr Med Res Opin.* 2004;20:1227–1233.

A preliminary, partial reanalysis of these data was presented at the Association for Research in Vision and Ophthalmology 2005 Meeting: D'Arienzo P, Granet D, Epstein AB, et al. Clinical efficacy of olopatadine and in epinastine allergic conjunctivitis subjects defined by sensitivity to conjunctival allergen challenge (CAC). *Invest Ophthalmol Vis Sci.* 2005;46:E-Abstract 2677. Available at: www.iovs.org. Accessed June 1, 2006.

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Conclusions: The results of this severity reanalysis support the original findings, suggesting that olopatadine is a more effective agent, as measured using severity scores, in the treatment of ocular itching and conjunctival redness compared with epinastine, even in patients with severe reactions. The results of the responder reanalysis suggest that more patients achieved total resolution of itching and conjunctival redness associated with allergic conjunctivitis with olopatadine treatment than with epinastine treatment. (*Clin Ther.* 2006; 28:1630–1638) Copyright © 2006 Excerpta Medica, Inc.

Key words: allergic conjunctivitis, olopatadine, epinastine, conjunctival allergen challenge, responder rates, symptom severity.

INTRODUCTION

Approximately 25% of the industrialized population is affected by allergic conjunctivitis, and the prevalence is rising.[1,2] Seasonal allergic conjunctivitis (SAC), an ocular hypersensitivity reaction elicited by exposure to seasonal allergens, is the most common form of allergic conjunctivitis. In most areas, the signs and symptoms of SAC are characteristically manifested during the spring, summer, and early fall months when pollen levels are high. Transient ocular itching and hyperemia are the primary sign and symptom, respectively, associated with SAC.[3] The degree of severity with which itching and redness are manifested varies among patients.

The pathophysiology of allergic conjunctivitis is mainly driven by mast cells. When allergens encounter the tear film, specific immunoglobulin (Ig) E antibodies are created and bind to the surface of the mast cells. On subsequent exposure, the IgE antibodies on the mast cells crosslink, initiating a cascade of intracellular events, which culminates in the activation of the mast cells and release of histamine and other proinflammatory mediators. Of all the many mediators involved in the allergic response, the clinical signs and symptoms are predominantly caused by histamine.[4]

There are a number of treatment options for allergic conjunctivitis. Although challenging, avoidance is the most effective step in blocking the allergic response. Refraining from mechanical rubbing, while important in limiting mast cell activation and further inoculation with allergen, can be unrealistic for a population struggling with unmitigated ocular itching. Other options include cold compresses or diluents, although these methods are neither highly effective nor practical. Topical antiallergic agents, such as antihistamines, mast cell stabilizers, and combination antihistamine/mast cell stabilizers, are commonly prescribed to manage the signs and symptoms of allergic conjunctivitis. The efficacy, comfort, and safety profiles of these agents vary greatly, which can make it difficult to select the optimal therapy for a particular patient.

Antihistamine/mast cell stabilizer combination agents are the newest class of antiallergics used for preventing and treating allergic conjunctivitis. Olopatadine hydrochloride, the first marketed combination antihistamine/mast cell stabilizer for ocular allergy, was approved in 1996 and is indicated for the treatment of the signs and symptoms of allergic conjunctivitis. As a histamine$_1$-selective antihistamine and human conjunctival mast cell stabilizer, olopatadine inhibits the release of histamine and other proinflammatory mediators from human conjunctival mast cells and blocks histamine response.[5–7] This multiacting agent provides rapid relief (often within 5 minutes), lasts up to 12 hours, and allows for better long-term management of ocular allergy symptoms.[8,9] When administered twice daily, olopatadine has been found to be effective and well tolerated in adults and children.[10,11]

Epinastine hydrochloride, another combination mast cell stabilizer/antihistamine, was first approved for the treatment of rhinitis in 1981. Since then, it has been prescribed as a treatment for rhinitis and other atopic diseases in Europe and Japan under the product names and formulations Flurinol (2-mg tablets), Alesion (0.2% oral liquid), and Talerc (10-mg tablets) (all, Allergan, Inc., Irvine, California).[12] In 2003, the US Food and Drug Administration (FDA) approved epinastine for the treatment of allergic conjunctivitis, and the drug is indicated for the prevention of itching associated with the disorder. It has been found to inhibit histamine release in rat peritoneal mast cells.[13] In a placebo-controlled study using conjunctival allergen challenge (CAC), epinastine was found to have antiitching efficacy, with early onset (3 minutes) and duration of action consistent with twice-daily dosing. In a randomized, placebo-controlled, environmental study comparing epinastine and levocabastine in 298 patients aged ≥9 years with allergic conjunctivitis, epinastine-treated patients reported significantly lower ocular itching scores compared with those receiving inactive solution ($P = 0.045$), and itching and hyperemia similar to those receiving levocabastine.[14]

The CAC model is an FDA-validated, standardized technique for the development and selection of antiallergic agents and the determination of their optimum concentrations that creates a precise and reproducible ocular allergic reaction.[15] The CAC model has been used in comparative studies of ophthalmic, nasal, and systemic antiallergic agents to evaluate efficacy, comfort, and onset and duration of action.

While the CAC model does not induce ocular allergic reactions in clinical practice, individuals experience symptoms of varying severity, just as symptom severity varies from patient to patient when allergen exposure is environmental. Consequently, it is possible to use the CAC model as a means of evaluating between-treatment differences in efficacy in treating the signs and symptoms of SAC based on the severity of patients' ocular allergic symptoms.

In a CAC trial comparing the effects of olopatadine and epinastine in 76 adults with allergic conjunctivitis, olopatadine-treated eyes exhibited significantly lower ocular itching scores than epinastine-treated eyes at 2 of 3 time points after allergen challenge (both, $P < 0.05$), and significantly lower conjunctival redness scores at 3 of 3 time points (all, $P < 0.001$).[16] The study assessed sign and/or symptom prevention by scheduling study medication instillation prior to allergen exposure, as opposed to measuring the reduction in severity of signs and/or symptoms by administering study drug after allergen exposure. The patients were grouped according to the severity of their ocular redness and itching symptoms, as determined by the mean symptom scores of both eyes, and treatment efficacy was assessed according to these mean values.

This post hoc analysis used data from the previous study to more precisely evaluate the efficacy of olopatadine and epinastine in alleviating various levels of severity of ocular itching and conjunctival redness and to determine whether there were any significant differences in the number of responders to treatment.

MATERIALS AND METHODS

Design

This post hoc analysis used data from a previous single-center, prospective, randomized, double-masked, contralateral-controlled, CAC study conducted at a clinic in North Andover, Massachusetts, in 2003.[16] The study was conducted in accordance with the Declaration of Helsinki[17] and the Good Clinical Practice[18] guidelines. All study-related procedures and ophthalmic examinations occurred in a clinic setting and were performed by qualified technicians and investigators. The informed-consent form and protocol for the study were approved by an independent institutional review board (IntegReview, Austin, Texas), and all patients provided written informed consent to the study procedures.

The clinical methodology of the study was previously published in detail.[16] The following is a brief review of that methodology (**Figure 1**).

Visit 1: Baseline Screening (Day 0)

At visit 1, patients were examined, visual acuity was tested, a baseline slit-lamp examination was performed, and patients were screened regarding inclusion and exclusion criteria. A bilateral CAC was performed with an allergen (eg, cat dander, pollen) to which the patient had had a positive result on previous skin testing. Patients who did not achieve a positive reaction were ineligible for the study.

Visit 2: Confirmatory (Day 7 ± 3)

At visit 2, patients were rescreened to confirm the results from visit 1. At 3, 5, and 7 minutes following allergen challenge, patients scored the severity of ocular itching using a 5-point standardized scale (0 = none to 4 = severe; half-point increments allowed). At 10, 15, and 20 minutes after challenge, the investigators assessed the severity of conjunctival redness and chemosis in each eye using the same scale. Patients with conjunctival redness and itching severity scores of ≥2 (at least moderate severity) were asked to return for visit 3.

Visit 3: Drug Evaluation (Day 21 ± 3)

At visit 3, medical and medication histories were updated and visual acuity was retested. A baseline slit-lamp examination was again performed. Following a review of inclusion and exclusion criteria, eligible patients were enrolled in the study and assigned a randomization number. Random assignment of patients to treatment groups and masking of study medication were performed by independent technicians who were not involved in any other aspect of the study. Commercially available samples of the study medications were obtained and provided in identical containers. Patients were assigned by randomization number, in an 8:1:1 ratio, to 1 of 3 treatment groups, as follows:

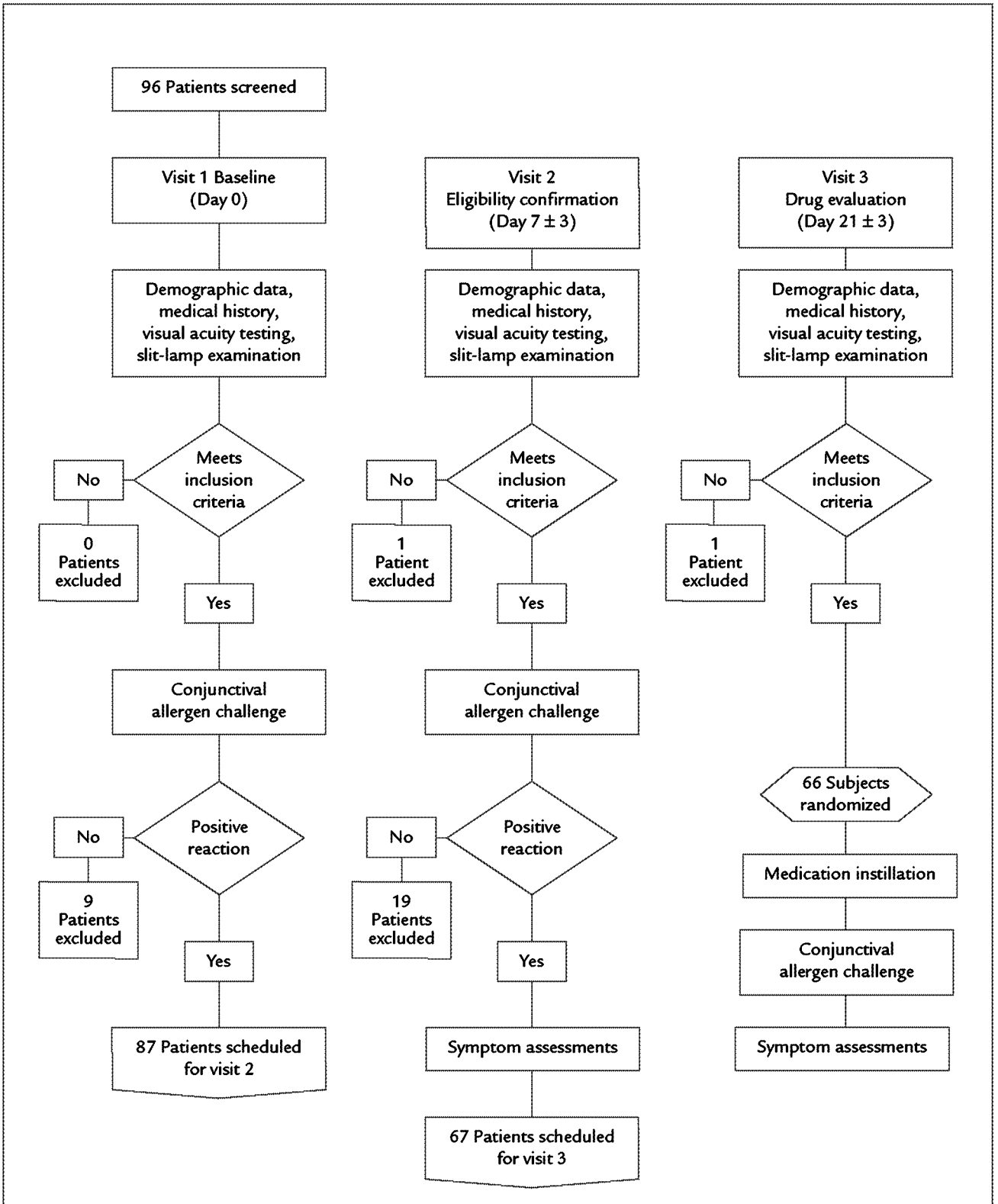


Figure 1. Study design.

- Olopatadine 0.1%* in 1 (left or right) eye and epinastine 0.05%† in the alternate eye;
- Olopatadine 0.1% in 1 eye (left or right) and inactive treatment (artificial tears) in the alternate eye; or
- Epinastine 0.05% in 1 eye (left or right) and artificial tears in the alternate eye.

The 2 placebo groups were included in the study design for validation purposes. One drop of each masked study medication was instilled by a technician into each eye according to the randomization code. Five minutes after medication instillation, CAC was performed bilaterally using the same allergen concentration that had elicited a positive result at visits 1 and 2. Subjective evaluations of itching and objective evaluations of redness and chemosis were performed at the same time points as described in visit 2.

Tolerability

Patients were observed as medication was instilled, and any spontaneous adverse effects (eg, burning, stinging) were considered related to treatment.

Statistical Analysis

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina), Excel 2003 (Redmond, Washington), and R version 2.2.1 (R Foundation for Statistical Computing).

Severity Analysis

Based on the severity scores for ocular itching and conjunctival redness at visit 2, each eye with a severity score of at least 2 was classified at each time point as moderate (score, 2), moderate/severe (score, 2.5), or severe (score, ≥3). The significance of between-treatment differences in severity at each time point was tested using the Wilcoxon rank sum test, with significance set at an α level of 0.05.

Responder Analysis

A *responder* was defined as an eye from the olopatadine/epinastine treatment group having a severity score of 0 for itching, redness, or both at ≥1 time point at visit 3. The significance of between-group differences in proportion of responders at each time point was tested using the Fisher exact test, with significance set at an α level of 0.05.

RESULTS

Ninety-six patients were screened at visit 1. Of those 96 screened, 87 patients qualified for visit 2. At visit 2, 19 patients were found ineligible because of an insufficient reaction to the CAC, and 1 patient discontinued due to personal reasons. At visit 3, 1 patient was disqualified due to having baseline allergic symptoms, and 66 patients (36 women, 30 men; mean age, 44.38 years [range, 20–71 years]) were randomized to receive drug. A total of 53 patients (106 eyes) were assigned to the olopatadine/epinastine treatment group; 6 patients (12 eyes), to the olopatadine/placebo treatment group; and 7 subjects (14 eyes), to the epinastine/placebo group.

Symptom Severity

Different eyes crossed severity groups at different time points (**Table**), but in general, there was a fairly even distribution across severity groups.

In all 3 categories of severity, olopatadine and epinastine were associated with some efficacy in relieving ocular itching and conjunctival redness. The mean (SD) itching severity score in the olopatadine-treated eyes was significantly lower compared with that of the epinastine-treated eyes in the moderate/severe group at 7 minutes after CAC (0.56 [0.73] vs 1.03 [0.76]; $P = 0.05$) and in the severe group at 5 and 7 minutes after CAC (5 minutes, 0.32 [0.48] vs 0.79 [0.75] [$P = 0.017$]; 7 minutes, 0.40 [0.99] vs 0.93 [0.84] [$P = 0.02$]) (**Figure 2A**). In addition, the mean conjunctival redness severity score was significantly lower in the olopatadine-treated eyes compared with the epinastine-treated eyes in the severe group at 10 minutes (1.47 [0.99] vs 2.29 [0.84]; $P = 0.032$). At the 20-minute assessment, conjunctival redness scores in the epinastine-treated eyes returned to near-baseline values (**Figure 2B**).

Response

For itching, the proportion of responder eyes was significantly greater with olopatadine treatment versus epinastine treatment at 7 minutes after CAC (27 [50.9%] vs 14 [26.4%]; $P = 0.016$). For conjunctival redness, at 15 and 20 minutes after CAC, the proportion of responder eyes was significantly greater with olopatadine treatment versus epinastine treatment

*Trademark: Patanol® (Alcon Inc., Fort Worth, Texas).
†Trademark: Elestat® (Allergan Inc., Irvine, California).

Table. Distribution of eyes across itching and conjunctival redness severity groups at visit 3.* Values are no. (%) of eyes.

Symptom/Sign/Time Point	Moderate	Moderate/Severe	Severe
Itching			
3 Min	25 (24)	32 (30)	26 (25)
5 Min	20 (19)	31 (29)	46 (43)
7 Min	24 (23)	32 (30)	44 (42)
Conjunctival Redness			
10 Min	27 (25)	20 (19)	28 (26)
15 Min	17 (16)	22 (21)	34 (32)
20 Min	32 (30)	14 (13)	32 (30)

*Includes the 53 patients (106 eyes) who received olopatadine in 1 eye and epinastine in the other. Severity was graded on a scale of 0–4, with 1/2-point increments: 2 = moderate; 2.5 = moderate/severe; 3–4 = severe.

(15 minutes, 12 [22.6%] vs 1 [1.9%] [$P = 0.002$]; 20 minutes, 10 [18.9%] vs 1 [1.9%] [$P = 0.008$]) (**Figure 3**).

Tolerability

There were no serious adverse events reported in this study. One patient in the olopatadine/epinastine treatment group reported mild, transient (~1-minute) stinging in the epinastine-treated eye immediately on instillation. No additional adverse events were reported.

DISCUSSION

When a patient presents with allergic conjunctivitis, both ocular itching and conjunctival redness are common, although the degree of severity may vary substantially. Consequently, it is valuable to compare ocular antiallergic therapies with respect to their ability to control signs and symptoms across severity groups, as well as to evaluate their ability to completely resolve itching and/or redness.

The results of the present post hoc analysis with regard to severity were consistent with the original (2004) findings,[16] suggesting that olopatadine is more efficacious in treating ocular itching and conjunctival redness compared with epinastine even as the severity of the reaction increases. In the responder analysis, for itching, there were nearly twice as many responders to olopatadine than to epinastine at the peak time point (7 minutes, which previous CAC studies found was the time of peak itching in this model[19]). For conjunctival redness, at different time points there were 3- to 6-fold as many responders to olopatadine treatment than epinastine treatment. Furthermore, at the 20-minute time point, redness scores in the epinastine-treated eyes returned to near-baseline values, suggesting that the ability of epinastine to treat conjunctival redness is short-lived.

It is not surprising that olopatadine was associated with higher response rates compared with epinastine, as these results are consistent with previous in vitro and in vivo studies in human conjunctival mast cells, which found that the mechanisms of action of olopatadine were as an antihistamine and mast cell stabilizer.[8] In in vitro studies in human conjunctival mast cells, the marketed concentrations of epinastine, azelastine, and ketotifen did not significantly inhibit histamine,[20] while olopatadine inhibited 96% of histamine release.[7] Furthermore, epinastine at its marketed concentration was found to cause considerable membrane disruption of mast cells, suggesting potential degranulation, while olopatadine did not cause this reaction.[20]

Although itching is the hallmark symptom, hyperemia is a common sign of ocular allergies.[21] Red eyes may cause social embarrassment for patients with allergy; thus the ideal therapy for ocular allergies must effectively address both itching and hyperemia. Dissatisfaction with a prescribed therapy may lead patients to self-medicate with over-the-counter treatments, increasing the risk for misuse or overuse of antiallergic therapies.

Although the CAC model is frequently used to evaluate therapies for ocular allergies, it is conceivable that the model is limited because of the disparity between amounts of allergen used in the CAC model

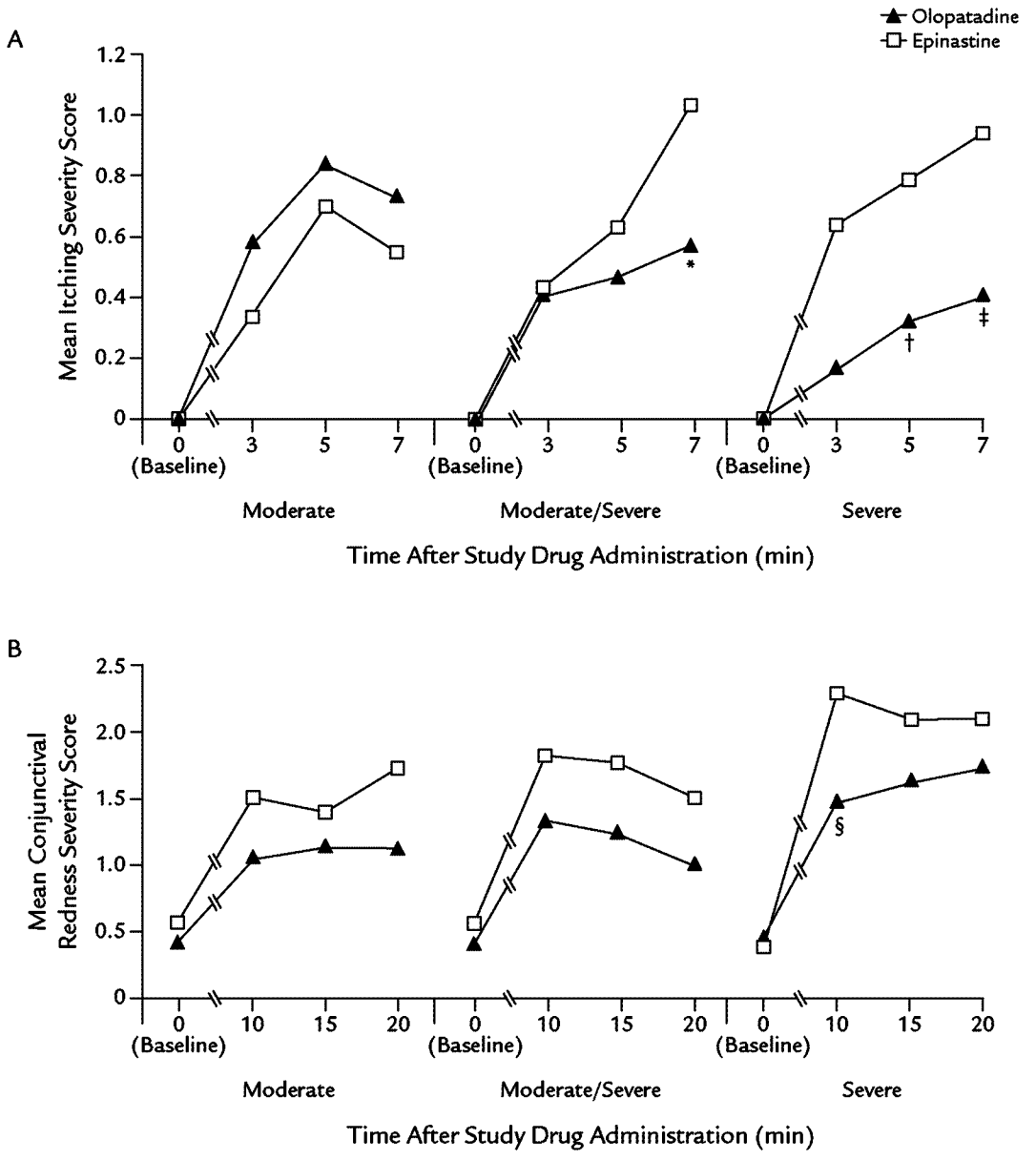


Figure 2. Mean severity scores for (A) itching and (B) conjunctival redness at visit 3 by severity category and treatment. Includes the 53 patients (106 eyes) who received olopatadine in 1 eye and epinastine in the other and had a conjunctival redness severity score ≥2 at visit 2. Scale: 0 = none to 4 = severe; half-point increments allowed. *$P = 0.05$ versus epinastine; †$P = 0.017$ versus epinastine; ‡$P = 0.02$ versus epinastine; §$P = 0.032$ versus epinastine.

versus clinical practice. In addition, although this study had a sufficiently large population to detect statistical significance, larger study populations would be beneficial in supporting the findings. Future studies may focus on the applicability of the responder and severity analyses as tools to measure clinical relevance of relative differences between treatments in clinical practice.

CONCLUSIONS

This small symptom-severity analysis found that olopatadine, with its antihistaminic and mast cell sta-

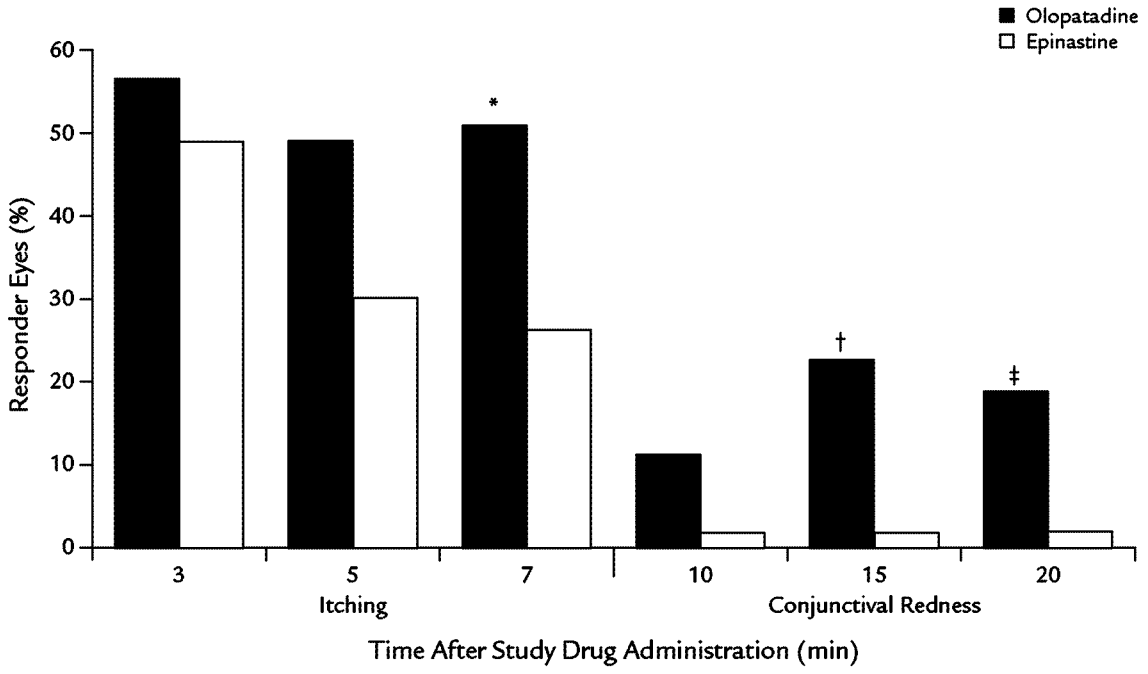


Figure 3. Responder analysis. Includes the 53 patients (106 eyes) who received olopatadine in 1 eye and epinastine in the other and had a conjunctival redness severity score ≥2 at visit 2. Scale: 0 = none to 4 = severe; half-point increments allowed. *Responder* was defined as a score of 0 (total resolution of symptoms) after medication instillation and challenge, at ≥1 time point, for itching (3, 5, 7 minutes) or redness (10, 15, 20 minutes) at visit 3. *P = 0.016 versus epinastine; †P = 0.002 versus epinastine; ‡P = 0.008 versus epinastine.

bilizing effects, was associated with more effective treatment of ocular itching, as measured using symptom severity scores, regardless of severity, compared with epinastine in these patients with ocular allergy. In addition, results from a responder analysis suggest that olopatadine was more effective, as measured using symptom severity scores, than epinastine at completely resolving ocular itching and redness associated with allergic conjunctivitis.

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