

Evaluation of the new ophthalmic antihistamine, 0.05% levocabastine, in the clinical allergen challenge model of allergic conjunctivitis

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The objective of this study was to evaluate the efficacy of 0.05% levocabastine, a new antihistamine formulated for ophthalmic use, compared with the placebo vehicle for the treatment of allergic conjunctivitis induced by ocular allergen challenge. Subjects who reacted positively in both eyes on two separate occasions to ocular allergen challenge with grass, ragweed, or cat dander (N = 47) received one dose of 1 to 2 drops of 0.05% levocabastine in one eye and its vehicle in the other eye. After 10 minutes, the predetermined dose of allergen was instilled in both eyes. Signs and symptoms of allergic conjunctivitis were evaluated with biomicroscopy and subjective evaluation of itching after 3, 5, and 10 minutes. Four hours after drug administration, subjects were rechallenged and reevaluated to determine levocabastine's duration of action. Results showed that levocabastine was significantly more effective than placebo in inhibiting itching, hyperemia, eyelid swelling, chemosis, and tearing after the initial challenge and in inhibiting all parameters except eyelid swelling after the rechallenge 4 hours later (p < 0.05). These results demonstrate that levocabastine, currently the only ophthalmic antihistamine available that is not combined with a vasoconstrictor, is efficacious in the inhibition of itching, as well as all of the allergic signs of a vascular origin, with a duration of action of at least 4 hours. Because of its strong effects on itching and hyperemia, chemosis, lid swelling, and tearing, levocabastine would be a valuable therapeutic agent to add to the heterogeneous family of antiallergic compounds presently available for the treatment of seasonal allergic conjunctivitis. (J ALLERGY CLIN IMMUNOL 1994;94:458-64.)

Key words: Levocabastine, allergen challenge, allergic conjunctivitis, type 1 hypersensitivity, clinical study

Allergic conjunctivitis can range in severity from relatively mild seasonal hay fever-type conjunctivitis to vernal keratoconjunctivitis and atopic keratoconjunctivitis, the more chronic condition, which can lead to structural changes and permanent scarring of the cornea.¹ The hallmark symptom of allergic conjunctivitis is itching, with additional definitive signs and symptoms including hyperemia, tearing, chemosis, and eyelid swelling.

Abbreviations used

AU: Allergen units
CPT: Conjunctival provocation test

The conjunctival provocation test has been an invaluable tool used for years in the study of the ocular allergic response.²⁻⁵ In addition, it has been used as a method of monitoring the local, ocular success of systemic immunotherapy,⁶ and recently, as a promising new method of local immunotherapy.⁷ Ocular allergen challenge has also proven to be an ideal instrument for the evaluation of new antiallergic agents.² It has been shown to elicit a bilaterally symmetrical ocular response, which reproduces the clinical course of events seen with a naturally occurring allergic reaction.^{2, 8} The model, as presented in this study, has proven to be safe and has permitted a reproducible, quantitative measurement of the allergic re-

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sponse with internal, contralateral controls, which allow a direct comparison between a drug-treated eye and a placebo-treated eye within the same individual.²⁻⁹ Furthermore, the allergen challenge model provides a uniquely simple means to accurately identify the duration of action of antiallergic compounds.¹⁰

In contrast, the evaluation of antiallergics in a seasonal environmental study of allergic conjunctivitis involves a large number of patients, and it is extremely difficult to demonstrate any statistically or clinically significant effect. Patients are typically entered into the study with their most severe signs and symptoms in order to qualify for entry and are then for 2 to 4 weeks, regardless of the natural progression of the disease. A variety of problems are encountered with this type of study design, which make it difficult to determine drug efficacy; these problems include the placebo acting as a tear substitute to dilute and wash away the allergen, the natural variability in environmental conditions and subject's exposure to them, and the lack of a suitable baseline. Use of the allergen challenge model eliminates these problems.

A multitude of less than ideal therapeutic agents is available for the treatment of seasonal allergic conjunctivitis. Although highly efficacious, topical steroids, with their narrow margin of safety, are a consequential choice for the treatment of ocular allergies that are less serious than vernal or atopic keratoconjunctivitis. Currently, no mast cell stabilizers are indicated for the treatment of seasonal or acute allergic conjunctivitis. Ophthalmic 4% sodium cromoglycate, a mast cell stabilizer, which is no longer available in the United States, was not indicated for treatment of seasonal allergic conjunctivitis, but for treatment of vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis, and giant papillary conjunctivitis.¹¹ Nevertheless, use of sodium cromoglycate has been investigated in numerous clinical studies and a wide range of ocular allergic diseases. A thorough search of the literature demonstrates that cromolyn has failed to produce clear results in environmental studies of seasonal allergic conjunctivitis^{12, 13} and in the antigen challenge model of acute allergic conjunctivitis.^{14, 15} Nonsteroidal antiinflammatory agents have recently been added to the class of antiallergics. This class of agents, however, is indicated only for the relief of ocular itching caused by seasonal allergic conjunctivitis.¹¹

The final class of agents available for the treat-

ment of seasonal allergic conjunctivitis is the antihistamines, which are currently only available in combination with vasoconstrictors. They have played an invaluable role in the treatment of ocular allergies, allowing physicians to either decrease or eliminate the use of topical steroids by providing additional symptomatic relief. The goal of treatment in seasonal allergic conjunctivitis should be to minimize the impact of the disease on the patient's lifestyle. If a highly efficacious antihistamine controls a patient's itching and redness more effectively than a mast cell stabilizer, the question of "symptomatic relief" versus "etiologic inhibition" of the allergic process becomes an argument of semantics.

Levocabastine is a newly synthesized histamine H₁ receptor antagonist. It is a very potent and specific antihistamine, which has been formulated for the treatment of seasonal allergic conjunctivitis. In the rat model of compound 48/80-induced mortality, levocabastine was 15,000 times more potent than chlorpheniramine.¹⁶ Orally administered levocabastine had the lowest median effective dose of 12 antihistamines tested in the 16-hour maximal inhibition of allergic wheal volumes in *Ascaris*-sensitive dogs.¹⁷ Ophthalmic levocabastine has been evaluated in patients with seasonal allergic conjunctivitis with promising results, compared with both placebo¹⁸ and sodium cromoglycate.¹⁹ It has also shown significant efficacy in the histamine and compound 48/80 models of allergic conjunctivitis in human beings.²⁰

The objective of this study was to evaluate the efficacy and duration of action of 0.05% levocabastine compared with the vehicle placebo for its ability to inhibit the signs and symptoms of allergic conjunctivitis induced by ocular allergen challenge in human volunteers.

METHODS

Subjects

All subjects read and signed an Informed Consent agreement approved by the Western Institutional Review Board (Olympia, Wash.) before entering the study. The following inclusion criteria had to be met by each subject: (1) ability and willingness to give consent; (2) ability and willingness to make all study visits; (3) ability to follow instructions; (4) age between 18 and 65 years; (5) successful challenge, inducing a score of at least 2+ in redness and itching in both eyes on two visits before drug administration; (6) a history of symptoms of clinically active seasonal allergic conjunctivitis; (7) positive diagnostic test results (skin and/or RAST) for allergic disease; and (8) willingness to avoid prohibited medication during the study period.

TABLE 1. Standardized grading system for the measurement of signs and symptoms of allergic conjunctivitis

Redness*†, Lid Swelling†
0 = None
1+ = Mild
2+ = Moderate
3+ = Severe
Chemosis*†
0 = None
1+ = Mild (detectable with slit lamp, conjunctiva separated from sclera)
2+ = Moderate (visually evident, raised conjunctiva, especially at limbal area)
3+ = Severe (ballooning of conjunctiva)
Tearing†
0 = None
1+ = Mild (eyes feel slightly watery)
2+ = Moderate (blow nose occasionally)
3+ = Severe (tears rolling down cheeks)
Itching (graded by subject)†
0 = None
1+ = Mild (intermittent tickling sensation)
2+ = Moderate (continual awareness but without the desire to rub eyes)
3+ = Severe (continual awareness with the desire to rub eyes)
4+ = Incapacitating (subject cannot resist urge to rub eyes)

*Photographs of each gradation are used as a guide.

†Increments of 0.5+ are allowed for each parameter.

In addition, no subject was allowed to enter the study if any of the following exclusion criteria were met: (1) presence of a bacterial or viral ocular infection; (2) presence of blepharitis, follicular conjunctivitis, iritis, or preauricular lymphadenopathy; (3) pregnancy or nursing or in women of childbearing potential use of inadequate contraceptive methods; (4) contraindications or known allergy to levocabastine; (5) wearing of contact lenses during the course of the study; (6) use of any systemic medication that might affect the test parameters; (7) presence of any significant illness that could be expected to interfere with the study, particularly any autoimmune disease (e.g., rheumatoid arthritis); (8) use of any topical ophthalmic solutions, including tear substitutes, during or for at least 2 weeks before the study; and (9) signs and symptoms of allergic conjunctivitis on taking the baseline examinations on days 1, 4, and 8. In addition subjects who were taking ophthalmic medications, which required longer than a 2-week washout period, were not included in the study.

Materials

Three types of allergens were used: Kentucky bluegrass (*Poa pratensis*; Hollister-Stier, Spokane, Wash.),

short ragweed (*Ambrosia artemisiifolia*; Hollister-Stier), and extract of cat dander (*Felis domesticus*; ALK America, Inc., Milford, Conn.). Six serial dilutions were prepared from the stock solution of bluegrass and ragweed (100,000 allergen units [AU] per milliliter), with final concentrations ranging from 19 to 625 AU per 25 ml dose. Four dilutions were prepared from the stock solution of cat allergen (50,000 AU/ml), with final concentrations ranging from 125 to 1250 AU per 25 ml dose. Phosphate-buffered saline was used as the diluent. All allergen solutions were reconstituted and diluted fresh daily on the morning of each visit.

Levocabastine suspension (0.5 mg/ml) was provided by Iolab Corporation (Claremont, Calif.). The placebo was the vehicle of the active preparation. Both active drug and placebo were packaged in identical nontransparent dropper bottles.

Procedure

This was a double-blind, paired comparison study in which each subject received levocabastine in one eye and placebo in the other eye in a randomized fashion.

Day 1, visit 1

Each subject's demographic, medical, and medication histories were taken, and informed consent was obtained. A baseline slit-lamp examination was performed to determine subject eligibility. If any subject exhibited signs of symptoms of allergic conjunctivitis in either eye, he or she was excluded from the study.

A conjunctival provocation test (CPT) was then performed in both eyes with allergens selected according to the results of skin or RAST tests. One 25 μ l drop of allergen in the lowest concentration was instilled into the conjunctival sac. If the subject did not react positively with a score of at least 2+ in hyperemia and itching in both eyes within the next 10 minutes, the next higher dose was instilled in the same manner. This was continued until the subject reacted positively with a score of at least 2+ in hyperemia and itching in both eyes. If the subject failed to react to any concentration, the subject was excluded from the study. Hyperemia and itching were graded with a standardized scale (Table 1). At the end of the visit, subjects received Vasocon-A (Iolab Corporation) to relieve any immediate discomfort caused by the allergic reaction.

Day 4, visit 2

In 3 days, the subjects returned to verify their positive CPT responses to the final allergen dose given at the initial visit. A slit-lamp examination was performed to exclude any subject who was currently exhibiting signs and symptoms of allergic conjunctivitis. The final dose of allergen that elicited the positive response at the initial visit was instilled in both eyes. Those subjects who met all of the entry criteria and again exhibited a positive 2+ CPT response in both eyes to this single dose of allergen were allowed to continue to day 8. Subjects were again given Vasocon-A at the end of the

TABLE II. Mean differences between eyes for signs and symptoms of ocular allergy

Parameter	Score in levocabastine-treated eyes minus score in placebo-treated eyes					
	Initial challenge			Rechallenge		
	3 Min	5 Min	10 Min	3 Min	5 Min	10 Min
Conj Red	-0.61	-0.50	-0.50	-0.27	-0.33	-0.24
<i>p</i> Value	<0.001*	<0.001*	0.001*	0.004*	0.004*	0.023*
Ciliary Red	-0.64	-0.55	-0.59	-0.34	-0.27	-0.26
<i>p</i> Value	<0.001*	<0.001*	<0.001*	0.003*	0.033*	0.045*
Epi Red	-0.45	-0.41	-0.46	-0.29	-0.31	-0.31
<i>p</i> Value	<0.001*	0.003*	0.002*	0.005*	0.015*	0.012*
Sum Red	-1.69	-1.47	-1.54	-0.89	-0.90	-0.81
<i>p</i> Value	<0.001*	<0.001*	<0.001*	0.002*	0.012*	0.017*
Itching	-1.28	-1.10	-0.95	-0.70	-0.68	-0.50
<i>p</i> Value	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.007*
Lid Swell	-0.18	-0.24	-0.36	-0.05	-0.14	-0.09
<i>p</i> Value	0.002*	0.001*	<0.001*	0.441	0.051	0.151
Chemosis	-0.40	-0.49	-0.52	-0.28	-0.39	-0.34
<i>p</i> Value	<0.001*	<0.001*	<0.001*	0.002*	<0.001*	0.002*
Tearing	-0.29	-0.46	-0.35	-0.17	-0.18	-0.19
<i>p</i> Value	0.045*	<0.001*	0.010*	0.084	0.074	0.038*

Conj. Red, Conjunctival hyperemia; *Ciliary Red*, ciliary hyperemia; *Epi Red*, episcleral hyperemia; *Lid Swell*, eyelid swelling.

*Statistically significant.

visit to relieve any immediate discomfort caused by the allergic reaction.

Day 8, visit 3

A baseline slit-lamp examination was performed to exclude any subjects who was currently exhibiting signs and symptoms of allergic conjunctivitis. Subjects then received, in double-masked, randomized fashion, 1 to 2 drops of 0.05% levocabastine suspension in one eye and the placebo in the other eye. Immediately after instillation of the study medication, the severity and duration of any stinging or burning, if present, was recorded. Ten minutes after instillation, the threshold allergen dose previously identified was administered in both eyes. After 3, 5, and 10 minutes, the investigator graded, by slit-lamp examination, the following allergic signs and symptoms with a standardized 4-point scale (Table I): conjunctival, ciliary, and episcleral hyperemia (all graded separately); eyelid swelling; chemosis; and tearing. Itching was graded by the subject at each time point with a 5-point scale (Table I). Purulent and mucous discharge were each evaluated by the investigator and recorded as present or absent. Photographs of each eye were taken after the 10-minute evaluation.

Four hours after drug instillation, the subjects were again challenged in both eyes with the same threshold dose of allergen. Measurements of the allergic signs and symptoms were repeated, as described above. Photographs of each eye were again taken after the 10-minute evaluation.

Statistics

The Wilcoxon matched-pair signed-rank test and the sign test were used to compare the paired treatment at the baseline examination and after each allergen challenge examination at 3, 5, and 10 minutes for each parameter except mucous and purulent discharge, for which the McNemar test was used. A "sum score" was generated by adding the three hyperemia scores together. The effect of placebo on decreasing the intensity of the allergic reaction by virtue of its action as a diluent was considered. Therefore to compare the levocabastine-treated eye to the placebo-treated eye, differences between means were generated by subtracting the placebo score from the levocabastine score.

RESULTS

Subject population

At visit 1, 65 subjects were initially challenged with antigen; 58 (89%) responded with a score of at least 2+ in itching and redness in both eyes. At visit 2, 57 of these 58 responders returned for a second challenge. A second positive bilateral allergen challenge response was observed in 48 of the 57 subjects (84%). On day 8, visit 3, all 48 subjects returned for the evaluation of drug efficacy. One subject was not challenged because he had taken a prohibited medication, which may have interfered with study results. The remaining 47 subjects completed the study.

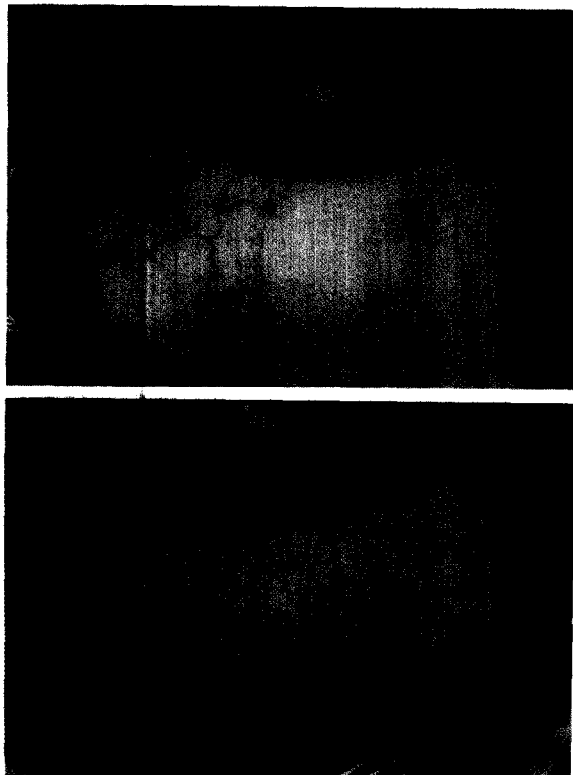


FIG. 1. Initial challenge. Eyes of one patient pretreated with one dose of levocabastine in one eye (**A**) and its vehicle placebo in the other eye (**B**) 10 minutes after allergen challenge. Levocabastine-treated eyes had significantly less itching, tearing, lid swelling, hyperemia (conjunctival, episcleral, ciliary, and the sum of all three) and chemosis than placebo-treated eyes after initial challenge (see Table II for p values).

The distribution of allergic sensitivity and specific allergens used for challenge in the remaining 47 subjects were as follows: cat dander, 21 subjects; grass, 9 subjects; and ragweed, 17 subjects. The mean age of the subjects was 33.2 years, with a range of 18 to 63 years. All subjects were white; 23 were female and 24 were male. All subjects had a normal ophthalmic history, and no subject had taken ophthalmic medications in the 4 weeks before the study.

Safety and tolerance

Stinging and burning were not observed in the majority of subjects (30 of 47) after levocabastine or placebo instillation. There were 16 reports of mild and one report of moderate stinging, with no significant differences seen between the incidence in drug-treated and placebo-treated eyes. There were no reports of systemic side effects or prolonged ocular allergic reactions after challenge.

Initial challenge

Table II summarizes all mean differences and corresponding p values for the score in treated eyes minus the score in control eyes at each time point and for each parameter after the initial challenge and the rechallenge 4 hours later.

Levocabastine was significantly better than placebo in the inhibition of conjunctival, episcleral, and ciliary hyperemia at all time points ($0.003 \geq p < 0.001$) (Fig. 1, *A* and *B*). Also, when the regional hyperemia scores were summed, yielding a score indicative of the general redness of the eye, levocabastine was significantly more effective than placebo ($p < 0.001$).

Significantly less itching ($p < 0.001$), lid swelling ($0.002 \geq p < 0.001$), chemosis ($p < 0.001$), and tearing ($0.045 \geq p < 0.001$) were also observed in the levocabastine-treated eyes at each of the three time points after challenge. There were no reports of mucous or purulent discharge in any subject after the initial challenge.

Mean differences for conjunctival, ciliary, and episcleral hyperemia, considered individually, ranged from -0.41 to -0.64 . The mean differences of the summed scores ranged from -1.47 to -1.69 . Itching mean differences ranged from -0.95 to -1.28 . For the remaining parameters (lid swelling, chemosis, and tearing), mean significant differences between the two groups ranged from -0.18 to -0.52 .

Four-hour rechallenge

When eyes were challenged again with allergen 4 hours after drug instillation, each of the regional hyperemia scores, as well as the summed scores, were still significantly improved in the eyes treated with levocabastine compared with eyes treated with placebo at all time points ($p \leq 0.045$). Itching ($p \leq 0.007$) and chemosis ($p \leq 0.002$) were also significantly inhibited by levocabastine at all time points after rechallenge. Tearing was significantly decreased in levocabastine-treated eyes only at 10 minutes ($p = 0.038$). Significant differences were not obtained from the lid swelling comparisons at any time point after rechallenge. Purulent discharge was not present in any subject at any time evaluated after allergen rechallenge.

Mucous discharge was observed in eight subjects at various postrechallenge examinations: 14 times in the levocabastine-treated eyes and 9 times in the placebo-treated eyes. In four of the eight subjects in whom mucous discharge was observed, it was present in both eyes. In the remaining four subjects, two reports of unilateral

discharge in the placebo-treated eye and one report of unilateral discharge in the drug-treated eye occurred. The paucity of these data prevented statistical analysis.

Mean differences after the rechallenge were less than those observed after the initial challenge. Individual hyperemia scores ranged from -0.24 to -0.34 , whereas summed hyperemia differences ranged from -0.81 to -0.90 . Mean differences for itching ranged between -0.50 and -0.70 . Mean differences for chemosis ranged from -0.28 to -0.39 , whereas the mean difference for tearing at 10 minutes, the only statistically significant finding in this parameter, was -0.19 .

DISCUSSION

Seasonal allergic conjunctivitis is a common ocular allergic disease seen by both the allergists and the ophthalmologist. This disease is the clinical result of mast cell degranulation triggered by IgE antibody-antigen interactions on mast cell membranes. Histamine, stored in the granules of mast cells and basophils, is the principle preformed mediator released from mast cells. In more complex and chronic diseases, such as vernal and atopic keratoconjunctivitis, this repetitive mast cell degranulation is considered the fountainhead from which a cascade of cellular and mediator-derived late-phase processes elaborate and amplify the inflammatory response. In comparison, considering the relatively unambiguous causes of seasonal allergic conjunctivitis, histamine is still, irrefutably, the most important mediator.

Histamine has been identified in normal tears (5 ng/ml) and in elevated concentrations in tears from patients with vernal keratoconjunctivitis (16 ng/ml).²¹ However, the high levels expected in tears of patients with acute allergic disease were not shown until a recent study identified the presence histaminase in human tears after conjunctival allergen challenge. Inactivation of these enzymes revealed that histamine is indeed elevated in tears of allergic patients after allergen challenge.²¹

In the conjunctiva only two histamine receptors, H_1 and H_2 , have been identified. H_1 receptor activation is primarily believed to induce itching²³ with some secondary effects on redness, whereas H_2 receptor activation primarily induces redness.²⁴ Antihistamines bind to these specific histamine receptors on effector cells without initiating a response. This reaction is one of competitive inhibition and is determined primarily by the concentration of the antihistamine drug at the

receptor site and also by the affinity of the antihistamine for this receptor.²⁵⁻²⁷ The antihistamines currently available for topical ophthalmic use (antazoline, pheniramine, pyrilamine) are all of the H_1 antagonist class, inhibiting itching, and are thus formulated in combination with vasoconstrictors such as naphazoline or phenylephrine for inhibition of redness. Of these combination agents, only Vasocon-A has received U.S. Food and Drug Administration approval for treatment of allergic conjunctivitis.¹¹

The results of this study show that levocabastine is a potent H_1 antagonist¹⁷ and is highly efficacious in the inhibition of itching at both the initial challenge and the rechallenge 4 hours later. More surprising were the effects of levocabastine on the allergic signs with a vascular origin. Levocabastine was significantly more effective than placebo in the inhibition of hyperemia, chemosis, tearing, and eyelid swelling at all time points after the initial challenge and in the inhibition of hyperemia and chemosis at all time points after the rechallenge. These results demonstrate that levocabastine has potent effects on the vasculature of the conjunctiva and is able to adequately reduce vasodilation. This finding was somewhat unexpected because it has been shown that levocabastine is a potent H_1 -receptor antagonist, whereas vasodilation, as previously mentioned, has traditionally been thought to be primarily the result of H_2 -receptor stimulation.²⁴ It is possible that because of the high potency of levocabastine as an H_1 antagonist, an effect on a lesser population of low-affinity H_1 receptors on blood vessels was revealed. These vascular H_1 receptors may play a role secondary to the more numerous H_2 receptors in allergic vasodilation. This effect has not been associated with other weaker antihistamines.²⁸ An alternative explanation of this effect is a direct action of levocabastine on the human mast cell. In previous studies the kinetics of its effects in the passive cutaneous anaphylaxis and *Ascaris* tests did suggest to the investigators that more than histamine antagonism was responsible for its antiallergic effects.¹⁷

Data from the allergen rechallenge demonstrated that levocabastine was still significantly effective 4 hours after administration. Although the drug effect was diminished, the smaller changes between eyes were also a reflection of the previously identified diminished response observed when a second challenge is performed on the same day.² All results were still highly consistent and statistically significant. The selection of 4 hours after drug administration as the duration-

of-action time point was conservative, because levocabastine has been shown in European studies to be effective in the treatment of allergic conjunctivitis with twice daily dosing^{18, 19, 29, 30} and is already approved as such in some countries.

In conclusion, these results showed that one dose of levocabastine was significantly effective in the inhibition of the signs and symptoms of allergen-induced allergic conjunctivitis, with a duration of action of at least 4 hours. Levocabastine comprehensively controlled not only itching but all of the vascular components of the allergic reaction. We propose that this effect may have been due either to the inhibition of lesser, low-affinity H₁ receptors on the conjunctival vasculature or to an as yet unrecognized direct action of levocabastine on the mast cell.

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