Allergology International. 2006;55:157-165

ORIGINAL ARTICLE

Efficacy of Levocabastine Hydrochloride Ophthalmic Suspension in the Conjunctival Allergen Challenge Test in Japanese Subjects with Seasonal Allergic Conjunctivitis

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ABSTRACT

Background: This study was conducted to investigate the efficacy and safety of 0.025% levocabastine hydrochloride in Japanese subjects with seasonal allergic conjunctivitis and its duration of action using the conjunctival allergen challenge (CAC) test.

Methods: Twenty-four asymptomatic subjects were randomized to instill 0.025% levocabastine ophthalmic suspension in one eye and vehicle in the other eye 10 minutes before the CAC test. Signs and symptoms of allergic conjunctivitis were scored 10, 15, and 25 minutes after the CAC test. The duration of drug effects was also evaluated by allergen rechallenge 4 hours after levocabastine administration. The itching score for each eye as the primary efficacy endpoint was assessed 15 minutes after the CAC test using a 5-point scale.

Results: The mean itching score in the levocabastine-treated group was 0.08 ± 0.06, which was significantly lower than the mean score of 1.98 ± 0.16 in the vehicle group (P<0.0001). The redness and chemosis of the conjunctiva were also improved significantly compared with the vehicle group. Levocabastine showed prolonged efficacy in inhibiting itching (0.42 ± 0.12 *vs* 0.94 ± 0.17, P<0.0002) and redness (1.04 ± 0.18 *vs* 1.42 ± 0.22, P < 0.01) of the conjunctiva upon the rechallenge test. No significant topical or systemic adverse safety findings were observed in the levocabastine group.

Conclusions: The results indicate that 0.025% levocabastine ophthalmic suspension is effective and safe in the treatment of allergic conjunctivitis with a duration of action of at least 4 h.

KEY WORDS

allergen challenge test, allergic conjunctivitis, conjunctival, itching, levocabastine hydrochloride, redness

INTRODUCTION

Levocabastine hydrochloride is an H_1-receptor antagonist developed by Janssen Pharmaceutica, Belgium.[1] A 0.05% ophthalmic suspension of this drug is useful in the treatment of allergic conjunctivitis.[2-5] In addition, a levocabastine nasal spray has been approved in Japan for the treatment of allergic rhinitis.

A double-blind clinical study was conducted in Japan with the objective of determining whether the optimal concentration of levocabastine ophthalmic solution is 0.025% or 0.05% in the treatment of allergic conjunctivitis.[6] The results of that study did not find a statistically significant difference between the two

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Received 3 August 2005. Accepted for publication 28 October 2005.

concentrations in terms of either the final global improvement rating or adverse reactions. In addition, when the 0.025% levocabastine ophthalmic suspension was compared with a disodium cromoglycate ophthalmic solution, they were found to be equivalent.[7] For that reason, in deference to safety concerns, the lower concentration of 0.025% was selected as the optimal concentration of this ophthalmic suspension in Japan. However, because that earlier study did not find any clear dose-response relationship and no comparison with a placebo was made, it was concluded that it was necessary to carry out a placebo-controlled, comparative, clinical study to demonstrate clearly whether 0.025% is the optimal concentration of this ophthalmic suspension for use in Japanese patients.

Type I allergy can be reproduced out of season using the conjunctival allergen challenge (CAC) test, which induces the signs and symptoms of acute seasonal allergic conjunctivitis. It has been reported that the CAC test reproduces both the early- and late-phase allergic ocular responses in a dose-dependent manner.[8-11] Accordingly, it was decided to conduct a clinical study of levocabastine ophthalmic suspension using the CAC test in individuals with a history of cedar pollinosis, which is a representative type of seasonal allergic conjunctivitis in Japan. The CAC test employed was that reported by Abelson *et al.*[12] and takes into account the reproducibility of the results and the safety of trial participants. This method is used extensively in Europe and the USA for assessment of the efficacy of ophthalmic agents.[13-15]

The present study was carried out as a placebo-controlled, double-blind, comparative study of the efficacy of 0.025% levocabastine ophthalmic suspension in inhibiting the ocular signs and symptoms elicited by the CAC test.

METHODS

PROTOCOL

This randomized, double-blind, placebo-controlled clinical study using the CAC test was conducted in compliance with the Japanese Good Clinical Practice Code of 1997, the institutional review board regulations, informed consent regulations, sponsor and investigator obligations, and the Declaration of Helsinki. Written, informed consent was obtained from all subjects before enrollment in the trial.

POPULATION

This clinical study was carried out at Hohsen Clinic, Research Center for Clinical Pharmacology, the Kitasato Institute (Tokyo, Japan), from November through December 1998. Subjects were enrolled in this study on the basis of satisfying the selection criteria while not falling within the scope of the exclusion criteria. Eligible subjects were asymptomatic but experienced seasonal allergic conjunctivitis caused by Japanese cedar pollen and were between the ages of 20 and 65 years. The inclusion criteria included a history of symptoms of allergic conjunctivitis during the Japanese cedar pollen season (February through April) and a positive result for cedar pollen in the assay for antigen-specific IgE antibodies using the CAP-RAST method.

Subjects were excluded from the study if they had any ocular disorder, including inflammation of the conjunctiva, cornea, or iris, and dry eye with a score of 5 mm or less in Schirmer's test, or any systemic disease, including asthma, any autoimmune disease such as rheumatoid arthritis, or any other significant illness. Subjects were also excluded if they had used a steroid preparation orally or subconjunctivally within 1 month before the first CAC test (step I), or an oral antihistamine, oral antiallergy drug, steroidal ophthalmic solution, antiallergy ophthalmic solution, vasoconstricting ophthalmic solution, nonsteroidal antiinflammatory drug ophthalmic solution, steroidal nasal spray, antiallergy nasal spray, or vasoconstricting nasal spray within 1 week before enrollment in the study.

The use of contact lenses was not permitted. Women who were pregnant, lactating, or possibly pregnant were excluded. Subjects who were allergic to antihistamines, antiallergy drugs, benzalkonium chloride, or glycerol were also excluded.

MEDICATIONS

The medications used in this study were 0.025% levocabastine ophthalmic suspension and the vehicle for 0.025% levocabastine ophthalmic suspension used as the placebo.

The allergen solution used for the CAC test was prepared from Allergen Scratch Extract Torii Cedar Pollen for Diagnostic Use that was a 20-fold dilution of a 50% glycerol NaCl solution (Torii & Co., Ltd., Tokyo, Japan). The control solution was prepared from Allergen Scratch Extract Torii Control Solution that was an aqueous solution containing 50% glycerol and 5% NaCl (Torii & Co., Ltd.). A phosphate-buffered saline solution (pH 7.0) was added to both the allergen solution and the control solution, followed by dialysis to prepare 50-fold, 100-fold, 200-fold, and 400-fold dilutions of the stock extract.

DESIGN

At the beginning of each step, the subjects underwent an ophthalmic examination that included baseline slit-lamp examination of visual acuity, intraocular pressure, and fundus examination. If the subjects exhibited any signs or symptoms of allergic conjunctivitis, they were excluded from this study. The safety of the medications was assessed in an ophthalmic evaluation (slit-lamp examination, intraocular pressure, visual acuity, fundus examination) and by systemic evaluation (hematology, blood chemistry panels, uri-

Table 1 Scoring of ocular symptoms: primary efficacy assessment endpoint.

Score	Symptom
Itching	
0:	None
1:	Mild (intermittent itching)
2:	Moderate (continuous itching)
3:	Severe (continuous itching with the desire to rub, normal functioning not impaired)
4:	Incapacitating (impairs subject's normal functioning)

Table 2 Scoring of ocular signs and symptoms: secondary efficacy assessment endpoints.

Score	Signs and symptoms
Redness	
Bulbar conjunctiva	
0:	None
1:	Mild (dilation of a few blood vessels)
2:	Moderate (dilation of many blood vessels)
3:	Severe (dilation of all blood vessels, white of the eye is hard to distinguish)
Palpebral conjunctiva	
0:	None
1:	Mild (dilation of a few blood vessels in part of palpebral conjunctiva)
2:	Moderate (dilation of many blood vessels in entire palpebral conjunctiva)
3:	Severe (redness of entire palpebral conjunctiva; individual blood vessels cannot be distinguished)
Chemosis	
Bulbar conjunctiva	
0:	None
1:	Mild (slight edema detectable only by slit lamp)
2:	Moderate (more diffuse edema visible in normal room light)
3:	Severe (ballooning of overall bulbar conjunctiva)
Palpebral conjunctiva (lid swelling)	
0:	None
1:	Mild (slight swelling of the palpebral conjunctiva)
2:	Moderate (diffuse swelling of the palpebral conjunctiva)
3:	Severe (bullous swelling of the palpebral conjunctiva)
Tearing	
0:	None
1:	Mild (eye feels slightly watery)
2:	Moderate (blows nose occasionally)
3:	Severe (tears overflow)
Discharge	
0:	Absent
1:	Present

nalysis, pulmonary function tests) .

Step I. Determination of Optimal Antigen Solution Concentration

Ten microliters of the lowest dilution (*i.e.*, 400-fold dilution) of the allergen was instilled into the right eye, while the same volume at the same dilution of the control solution was instilled into the left eye. If no reaction occurred in the right eye within 10 minutes, increasing dilutions of the allergen were administered every 10 minutes until a positive reaction as defined by an itching score of at least 2 was elicited in the right eye. Redness, chemosis, tearing, and discharge were also assessed. The criteria for the scoring of ocular symptoms and signs are listed in Tables 1,2.

Subjects who failed to respond to any dilution of the allergen in the right eye or responded to the allergen control solution in the left eye were excluded

from the study.

Step II. Confirmation of Antigen Challenge Response and Determination of Observation Time

Ten microliters of the appropriate dilution of the allergen determined in step I was instilled into both eyes of each subject. Itching, redness, chemosis, tearing, and discharge were scored and recorded every 5 minutes for 30 minutes after the instillation of the allergen. If an itching score of at least 2 was present in both eyes, the subject was eligible for study enrollment and instructed to participate in step III.

The main observation time used in step III was the time when the highest total score calculated for itching at each of the six observation time points was recorded. On the basis of the time-course patterns of the total score for all other signs and symptoms, two other observation times were determined for use in step III.

Step III. Administration of Drugs

Each study solution was randomly assigned to one of the eyes of each subject, *i.e.*, 0.025% levocabastine ophthalmic suspension to one and the vehicle to the other eye. Two drops of each solution were instilled into the respective eyes. The allergen at the predetermined dilution was instilled into both eyes 10 minutes after 0.025% levocabastine ophthalmic suspension instillation. The signs and symptoms of allergic conjunctivitis were scored at the observation time determined in step II. Itching is the most frequent symptom in patients with allergic conjunctivitis, and thus in this study the itching score was evaluated as the primary efficacy assessment endpoint. The subjects were rechallenged 4 hours after drug administration to assess the duration of action of each agent. The signs and symptoms were scored at the same three observation times that were employed after the first challenge.

SAFETY

"Adverse events" were defined as any associated ocular or systemic symptoms or signs that manifested after the administration of the study medications. "Adverse reactions" were defined as adverse events for which a cause-effect relationship with the administered study medication was unable to be ruled out. An overall evaluation was made of the safety of the administered study medication on the basis of global evaluation of the presence or absence of adverse drug reactions and their severity.

STATISTICAL ANALYSIS

The Wilcoxon matched paired signed-rank test was used to compare the paired treatment as the baseline examination and after each allergen challenge examination. Mean differences were generated by subtracting the levocabastine score from the vehicle score in the statistical analysis. A probability value of less than 0.05 was considered statistically significant, and data are expressed as mean ± standard error of the mean.

Table 3 Demographic characteristics in step III.

Patients (no.)	24
Gender	
Male	23
Female	1
Age (years)	
Mean ± SE	24.8 ± 1.02
(minimum − maximum)	(20 − 40)
Peak symptom season (no.)	
Spring only	23
Spring + autumn	1
Complications (no.)	
General (excluding ocular symptoms)	
None	22
Allergic rhinitis	2

RANDOMIZATION AND STUDY MASKING

Each study medication was randomly assigned to be administered to the left and right eyes so that biases could be excluded. Study medications were filled in white, translucent, polyethylene bottles with the same outer appearance and wrapped in shrink film, and one bottle of each was placed in a white box stamped with a drug number. One box represented the drug supply for one study subject. In addition, the instillation of the study medications to the eyes was performed by the study assistants (nurses), and the investigators who performed the evaluations were not permitted to enter the room while the study medications were being instilled and/or the test bottles were transported to the room or while the bottles remained there before or after instillation. Moreover, the study subjects were also unable to distinguish between the two study medication preparations based on the appearance of the bottles, and it was impossible for the subjects to see the liquids and distinguish between them while they were being instilled. As a result of these precautions and countermeasures, both the investigators and study subjects were blinded to which study solutions were administered.

RESULTS

NUMBER OF SUBJECTS IN EACH STEP AND BACKGROUND CHARACTERISTICS

Of the 45 subjects included in step I, one developed a mild itching score for the right eye in which the allergen solution was instilled, as well as a moderate itching score for the left eye in which the allergen control solution was instilled. In addition, one exhibited moderate itching in the left eye and three did not experience moderate or more severe itching in the right eye. Redness in the left eye was reported for one sub-

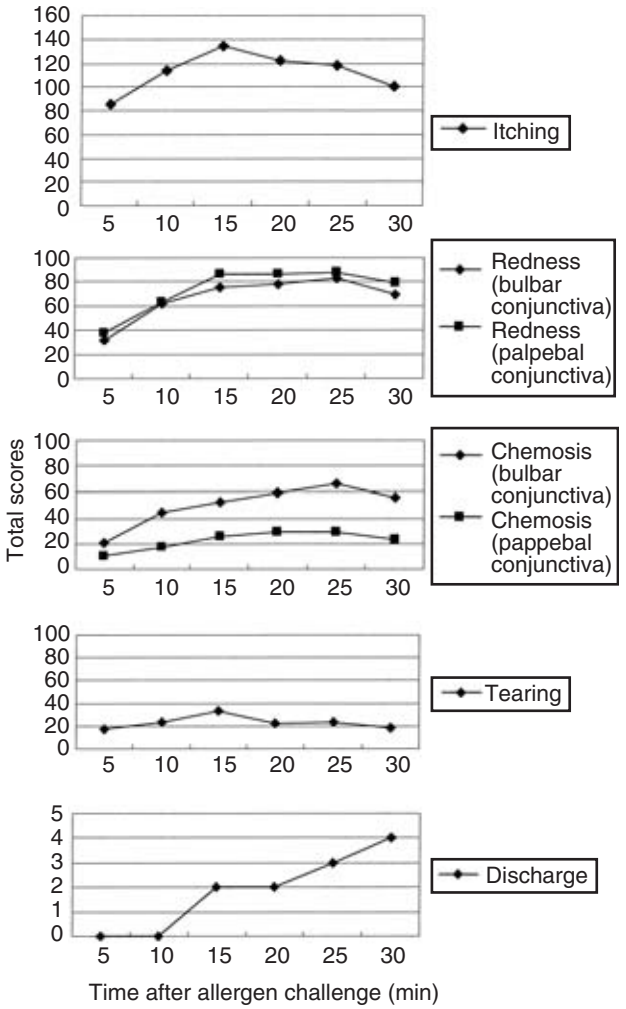

Fig. 1 Time-course change in total scores for each sign and symptom after allergen challenge in step II (n = 58 eyes of 29 patients).

ject. Moreover, one subject was involved in a traffic accident after the completion of step I and had to drop out. After exclusion of these seven participants, 38 proceeded to step II.

In step II, moderate or more severe itching of both eyes was observed in 29 subjects (76.3%), and 25 were selected for step III because they had the largest number and highest severity scores of manifested signs and symptoms. However, an investigation performed immediately prior to the start of step III revealed that one of the selected subjects was also participating in another clinical study on an exclusion criterion. Accordingly, the final total enrolled in step III was 24 subjects.

Table 3 shows demographic characteristics of the subjects in step III. The 24 subjects consisted of 23 men and one woman, with a mean age of 24.8 ± 1.02 years. The CAP-RAST test yielded positive reactions for cedar pollen in 24, for mugwort in six, for ragweed in eight, for mites in 12, and for house dust in 14 subjects.

Step II. Determination of Observation Time for Step III

In step II, the highest total score for itching occurred 15 minutes after instillation of the allergen solution (Fig. 1). This time was thus selected as the main observation time point to be used in step III. In addition, the peak scores for both redness and chemosis of the bulbar conjunctiva occurred 25 minutes after allergen solution instillation in step II. Thus, 25 minutes was another observation time point in step III, and this was further supplemented by the 10-minute time point, which was employed in the study by Abelson *et al.*[4] Thus, a total of three observation time points were employed in step III: 10, 15, and 25 minutes after instillation of the allergen (Fig. 2).

Step III. Efficacy of Levocabastine

The mean itching score was 0.08 ± 0.06 in the 0.025% levocabastine-treated group (eyes) and 1.98 ± 0.16 in the vehicle group (eyes). The score was significantly lower in the 0.025% levocabastine-treated group compared with the vehicle group at 15 minutes after the initial allergen challenge ($P < 0.0001$). Even at 10 (0.19 ± 0.08 *vs* 1.94 ± 0.20, $P < 0.0001$) and 25 minutes (0 ± 0 *vs* 1.44 ± 0.22, $P < 0.0001$) after the allergen challenge, the mean itching score was significantly lower in the 0.025% levocabastine-treated group (Table 4). Allergic symptoms in the secondary efficacy assessment endpoints, *i.e.*, redness of the bulbar conjunctiva (0.79 ± 0.17 *vs* 1.67 ± 0.26, $P < 0.0003$) (Table 5) and chemosis of the bulbar conjunctiva (0.29 ± 0.09 *vs* 0.83 ± 0.21, $P < 0.0039$), were significantly improved in the 0.025% levocabastine-treated group compared with the vehicle group. The 0.025% levocabastine ophthalmic suspension was significantly more effective than the vehicle in inhibiting the itching (0.42 ± 0.12 *vs* 0.94 ± 0.17, $P<0.0002$) and redness of the bulbar conjunctiva (1.04 ± 0.18 *vs* 1.42 ± 0.22, $P <0.01$) upon rechallenge 4 hours after study medication instillation.

SAFETY

Adverse reactions for which a cause-effect relationship with the study medication could not be ruled out totaled four events in three subjects. The diagnosed adverse drug reactions consisted of one event each of tearing and irritation of the eye, and itching in one eye administered the levocabastine ophthalmic suspension, and one event of irritation in one eye administered the vehicle. All of these adverse drug reactions were mild in severity, and their prevalence was low. There were no cases of a problem in terms of safety as a result of administration of the 0.025% levo-

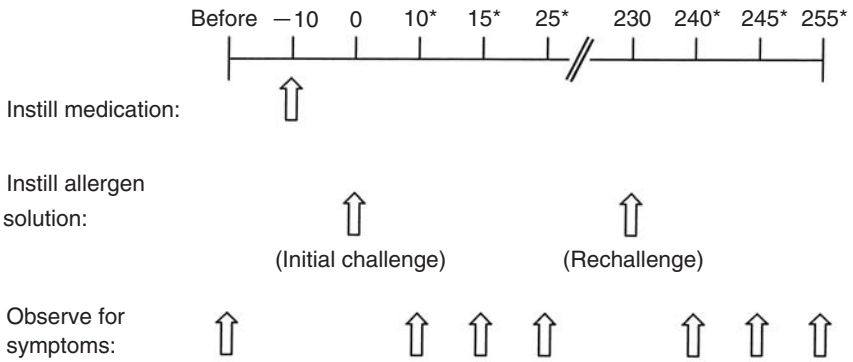

Fig. 2 Schedule of administration of study drug and vehicle and observations for step III. *Observation time points were determined based on the results recorded in step II.

Table 4 Itching scores after conjunctival allergen challenge.

First challenge	3	2.5	2	1.5	1	0.5	0	Mean score ± SE
Baseline								
Levocabastine	0	0	0	0	1	0	23	0.04 ± 0.04
Vehicle	0	0	0	0	0	0	24	0.00 ± 0.00
10 min								
Levocabastine	0	0	0	0	4	1	19	0.19 ± 0.08**
Vehicle	7	1	10	0	3	0	3	1.94 ±0.20
15 min								
Levocabastine	0	0	0	0	2	0	22	0.08 ± 0.06**
Vehicle	6	1	10	2	4	0	1	1.98 ± 0.16
25 min								
Levocabastine	0	0	0	0	0	0	24	0.00 ± 0.00**
Vehicle	4	1	7	0	6	0	6	1.44 ± 0.22
Rechallenge	3	2.5	2	1.5	1	0.5	0	Mean score ± SE
Baseline								
Levocabastine	0	0	0	0	0	0	24	0.00 ± 0.00
Vehicle	0	0	0	0	0	0	24	0.00 ± 0.00
10 min								
Levocabastine	0	0	2	0	7	2	13	0.50 ± 0.13*
Vehicle	2	0	5	1	7	1	8	1.04 ± 0.20
15 min								
Levocabastine	0	0	1	0	8	0	15	0.42 ± 0.12**
Vehicle	0	0	7	0	8	1	8	0.94 ± 0.17
25 min								
Levocabastine	0	0	1	0	3	0	20	0.21 ± 0.10**
Vehicle	0	0	4	0	10	1	9	0.77 ± 0.15

Significant difference compared with vehicle: *$P < 0.01$, **$P < 0.001$.

cabastine ophthalmic suspension. No subject showed deviation from the standard ranges of values for the parameters in the physiologic tests.

DISCUSSION

In the USA and Europe, 0.05% levocabastine suspension is exclusively available for the treatment of allergic conjunctivitis. However, the results of a clinical study conducted in Japan[6] showed that there was no statistically significant difference between the 0.025% and 0.05% preparations. Therefore, we designed this study to evaluate the clinical efficacy of 0.025% levocabastine suspension for the treatment of allergic conjunctivitis.

In comparison with vehicle, this study found that the 0.025% levocabastine ophthalmic suspension

Table 5 Redness scores in the bulbar conjunctiva after conjunctival allergen challenge.

First challenge	3	2	1	0	Mean score ± SE
Baseline					
Levocabastine	0	0	0	24	0.00 ± 0.00
Vehicle	0	0	0	24	0.00 ± 0.00
10 min					
Levocabastine	0	4	8	12	0.67 ± 0.16**
Vehicle	4	9	4	7	1.42 ± 0.22
15 min					
Levocabastine	0	6	7	11	0.79 ± 0.17**
Vehicle	9	5	3	7	1.67 ± 0.26
25 min					
Levocabastine	1	6	5	12	0.83 ± 0.20**
Vehicle	8	6	4	6	1.67 ± 0.25
Rechallenge	3	2	1	0	Mean score ± SE
Baseline					
Levocabastine	0	0	4	20	0.17 ± 0.08
Vehicle	0	0	3	21	0.13 ± 0.07
10 min					
Levocabastine	0	5	11	8	0.88 ± 0.15*
Vehicle	1	11	5	7	1.25 ± 0.19
15 min					
Levocabastine	1	6	10	7	1.04 ± 0.18**
Vehicle	4	8	6	6	1.42 ± 0.22
25 min					
Levocabastine	1	3	12	8	0.88 ± 0.16**
Vehicle	2	9	6	7	1.25 ± 0.20

Significant difference compared with vehicle: * $P < 0.01$; ** $P < 0.001$.

showed significant inhibition of the itching and redness of the eyes that are the principal symptoms of allergic conjunctivitis and significant inhibition of the manifestation of symptoms continued even 4 hours after the second allergen challenge. Because no safety problems were noted, these study results indicate that the 0.025% levocabastine ophthalmic suspension, which exhibits antihistamine activity, is a useful therapy for allergic conjunctivitis.

When conducting clinical research on allergic conjunctivitis, it is necessary to minimize the variation in the environmental factors that influence the degree of allergen exposure. However, it is difficult to carry out a placebo-controlled comparison of an investigational ophthalmic solution successfully under constant natural conditions since the manifestation of signs and symptoms would be influenced by the inevitable fluctuations in the levels of allergens due to various uncontrollable outside factors.[16] In this context, the best approach for evaluating the efficacy of levocabastine ophthalmic suspension in comparison with vehicle is to employ the CAC test.

In step III in the present study, when the effects of levocabastine ophthalmic suspension and vehicle were compared in the test, the CAC study medication was administered first, followed by challenge with the allergen solution 10 minutes later, and then a rechallenge was performed after a further 4 h. This method, established by Abelson *et al.*,[12] allows confirmation of both the onset and duration of action of a test drug in a single challenge test. We selected the same method with the objective of standardizing the conditions of our study with those of earlier studies.

In step I of this study, which was performed to determine the optimal concentration of the challenge allergen solution, we initiated the allergen challenge using a 400-fold dilution of a commercial cedar pollen solution. This represents a low concentration, corresponding to only about one-half of the concentrations employed in earlier studies performed in Japan.[17] As a result of this approach, there were no cases of adverse events in this study that could be considered a clinical problem, indicating that our method permits ocular challenge tests to be carried out safely.

Abelson *et al.*[12] reported performing ocular challenges in approximately 950 subjects, with one case of mild bronchial constriction without wheezing in an asthmatic patient, and three cases of urticaria and periorbital swelling. However, in steps I and II in our present study, conducted to establish the allergen

concentration to be used, the observed adverse events were mainly ocular and nasal symptoms, while there were no systemic allergic symptoms. Moreover, since almost all of the symptoms disappeared on the day of the challenge test or on the following day, it can be concluded that our study was safe.

There is also the concern that if the glycerol included in the scratch extract remains in the allergen solution, it will not be possible to observe clearly the ocular allergic symptoms due to the allergen because of simultaneously occurring signs and symptoms caused by the irritation arising from the glycerol. For this reason, the permissible level of glycerol in the allergen solution was set at less than 2%.

Cedar pollen was employed as the challenge allergen, and the positive response rates of the study subjects were 86.7% (39/45) in step I and 76.3% (29/38) in step II, respectively. Abelson *et al.*[12] reported using cat hair and dander, grass pollen, and ragweed pollen as allergens in their challenge tests, and the response rates were 83.6% (331/396) in step I and 87.2% (232/266) in step II. The response rates in our study were thus almost the same as those reported by Abelson *et al.*, and we conclude that the challenge response in our study was sufficient.

In clinical studies carried out on levocabastine ophthalmic suspensions in Japan for the treatment of allergic conjunctivitis,[6,7,18] the principal symptom was itching, while the main clinical sign was redness. Since most patients in those earlier studies experienced itching, this symptom was selected for use as the primary efficacy assessment endpoint in the present study. Moreover, since this was the first study in Japan in which the ocular challenge test was employed with the objective of performing a randomized, double-blind, placebo-controlled (comparative) study of the efficacy of a drug, we used step I to identify the optimal allergen concentration in each study subject and then proceeded to step II to confirm the reproducibility of the allergic response induced. In step II, we also analyzed the time-course profile of the allergic response by observing the signs and symptoms of the subjects at 5-minute intervals and then calculated the total score for each sign and symptom at each observation time point so that we could identify the time of maximal intensity of each. The results of the time-course profiles revealed that the highest total score for the symptoms of itching and tearing occurred 15 minutes after instillation of the challenge allergen solution, whereas the signs of redness, chemosis, and lid swelling each showed maximal intensities 25 minutes after challenge (Fig. 1). Accordingly, 15 minutes was stipulated as the main observation time point since itching was the primary efficacy assessment endpoint.

In the 24 subjects who participated in step III, which was the drug administration phase of our study, the 0.025% levocabastine ophthalmic suspension showed efficacy by significantly inhibiting itching in comparison with the vehicle. This statistically significant inhibition was seen not only at 15 minutes postchallenge but also at each of the other observation time points. Moreover, the 0.025% levocabastine suspension showed almost 2 units of inhibition of itching compared with the vehicle, and most subjects reported no itching in levocabastine-instilled eyes. Therefore, we concluded that 0.025% levocabastine eyedrops are clinically significantly effective. Redness was also significantly inhibited by the 0.025% levocabastine ophthalmic suspension in comparison with the vehicle at each of the three observation time points. Manifestation of the signs and symptoms of tearing and lid swelling after allergen challenge occurred in only a small number of the study participants, and it was thus not possible to perform an accurate or valid comparison of the efficacy of the 0.025% levocabastine ophthalmic suspension and the vehicle in relation to these two evaluation parameters. The observations performed after rechallenge of the experimental subjects 4 hours after drug administration revealed that the 0.025% levocabastine ophthalmic suspension still showed significant inhibition of the itching and redness of allergic conjunctivitis in comparison with the vehicle. These findings are evidence that the effects of the 0.025% levocabastine ophthalmic suspension persist for a relatively long period after administration of the drug to the eyes.

When considered together with the results reported for the early phase II clinical study performed with levocabastine ophthalmic suspensions, the results of the present study support the appropriateness of the 0.025% concentration of levocabastine ophthalmic suspension for clinical use.

ACKNOWLEDGEMENTS

This study was sponsored by Janssen Pharmaceutical KK, Tokyo, Japan, and the authors thank Hiromasa Takahashi and Tatsumi Nakashima, Janssen Pharmaceutical KK, for assistance.

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