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Original article

Evaluating the efficacy of epinastine ophthalmic solution using a conjunctivitis allergen challenge model in patients with birch pollen allergic conjunctivitis

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Abbreviations:

CAC	conjunctival allergen challenge
SAC	seasonal allergic conjunctivitis
H1	histamine 1
OAS	oral allergy syndrome

ABSTRACT

Background: The efficacy of epinastine 0.05% ophthalmic solution for pollen allergic conjunctivitis has already been shown in a conjunctival allergen challenge (CAC) test using cedar pollen as a challenge. The present study investigated the efficacy of this solution against birch pollen conjunctivitis in a CAC test.
Methods: Ten adult subjects (eight males and two females) with asymptomatic birch pollen conjunctivitis were enrolled in this study. The average age of the subjects was 41.1 years. This study was conducted during a period without birch pollen dispersion. In each subject, the epinastine 0.05% ophthalmic solution was instilled in one eye, and an artificial tear fluid was instilled in the fellow eye in a double-blind manner. Five minutes or 4 h after the drug instillation, both eyes were challenged with an optimal concentration of birch pollen, and ocular itching and conjunctival hyperemia were then graded. Tears were collected before the drug instillation and 20 min after the pollen challenge, and the histamine level was measured.
Results: The ocular itching scores and palpebral conjunctival hyperemia scores of the epinastine-treated eyes were significantly lower than those of the contralateral control eyes when the eyes were pretreated with the drug 4 h before the CAC. There was a significant correlation between the tear histamine level and mean ocular itching score of three time points (3, 5 and 10 min) following the CAC in the control eyes but not the epinastine-treated eyes.
Conclusions: Epinastine is effective in suppressing ocular itching and conjunctival hyperemia in birch pollen conjunctivitis.

Introduction

Allergic conjunctivitis is a conjunctival inflammatory disease associated with a type 1 allergy.[1] It is classified as seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis. Various species of pollen can be causative antigens of SAC, and variation of pollen depends on the region and season. Cedar pollen is the most common antigen for SAC in Japan, except for Hokkaido prefecture in the north of Japan. In Hokkaido, birch pollen is the most common antigen of SAC,[2] and the birch pollen-related SAC season lasts almost one month, from the end of April to the beginning of June. Birch pollen is also a major allergen trigger in the spring in Europe and North America.[3]

Eye drops containing antiallergic ophthalmic solutions are the main treatment for allergic conjunctivitis. Epinastine has both effects of antihistamine properties, blocking the histamine 1 (H1) receptor,[4] and chemical mediator stabilizer properties, inhibiting the release of mediators, including histamine and leukotrienes.[5,6] A phase III study demonstrated that epinastine 0.05% ophthalmic solution was effective in suppressing SAC symptoms in patients in a conjunctival allergen challenge (CAC) test using an allergen solution of cedar pollen.[7] To our knowledge, the efficacy of epinastine 0.05% ophthalmic solution in treating SAC caused by other antigens has not been studied. In this study, its efficacy was examined in a CAC test using birch pollen in humans.

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Table 1
Grading of ocular itching and palpebral and bulbar conjunctival hyperemia.

Scale	Symptoms
Ocular itching	
0:	None
1:	Intermittent itching
2:	Continuous itching
3:	Continuous itching with the desire to rub, normal functioning not impaired
4:	Incapacitating (impairs subject's normal functioning)
Palpebral and bulbar conjunctival hyperemia	
0:	None
1:	Dilation of a few blood vessels in part of the palpebral/bulbar conjunctiva
2:	Dilation of many blood vessels in the entire palpebral/bulbar conjunctiva
3:	Redness of entire palpebral/bulbar conjunctiva/individual blood vessels cannot be distinguished

Methods

Subjects

Thirty-six healthy adult volunteers with a history of birch pollen allergic conjunctivitis and no ocular symptoms were selected from December 2014 to February 2015 (outside the birch pollen season). The study was approved by the ethics committee of Hokkaido University Hospital (approval number 014-0193) and carried out in accordance with the Declaration of Helsinki and Ethical Guideline for Clinical Studies stipulated by the Ministry of Health, Labor and Welfare, Japan. All the patients who participated in this study provided written consent after they received oral and written information about the study. The study was registered at https://center.umin.ac.jp with the ID code UMIN000015797.

This was a prospective, double-masked, randomized, placebo-controlled, single-center (Hokkaido University Hospital, Hokkaido, Japan) study.

Allergen solution

An allergen solution was prepared from glycerol 1:20 w/v birch pollen extract solution (Birch Mix PRW HollisterStier, Spokane, WA). Before the challenge tests, the extract was diluted with a diluent of chondroitin sulfate 1:100 w/v, NaCl 2:10,000 w/v and glycerol 2:100 w/v. Diluted allergen solution was prepared at different concentrations (25-fold, 50-fold, 100-fold, and 200-fold).

CAC

The clinical methodology and grading system for allergic conjunctivitis followed those reported earlier.[7,8] The optimal concentration of the allergen solution was determined individually at the second visit. The allergen solution was instilled into the subject's eye, and the severity of ocular itching and palpebral and bulbar conjunctival hyperemia was evaluated according to the previous study.[7] Table 1 shows the grading of ocular allergic symptoms (ocular itching and conjunctival hyperemia).

Clinical trial design

Figure 1 shows the outline of this study. For the duration of the study, the subjects were instructed not to use corticosteroids, antiallergic drugs, immune suppressants, or immunomodulation therapy, topically nor systemically, and subjects who experienced ocular allergic symptoms including ocular itching and conjunctival hyperemia before the CAC were excluded.

At visit 1, after written informed consent was obtained, subjects were excluded according to demographic data such as age (20>, 65<) and pregnancy. Subjects who had a negative response to serum birch pollen-specific Immunoglobulin E (IgE) in a capsulated hydrophilic carrier polymer radioallergosorbent test were excluded from the study.

At visit 2, CAC tests were performed according to the previous study.[7] After the allergen control solution (Allergen Scratch Extract Torii Control Solution, Torii Pharmaceutical, Tokyo, Japan) was instilled into the conjunctiva to exclude subjects who showed a conjunctival inflammatory reaction to the allergen solution without pollen antigen, 30 μL of the lowest allergen solution was instilled into each eye. The allergen concentration was increased until an ocular itching score of at least 2 (continuous itching) was recorded and both palpebral and bulbar conjunctival hyperemia scores of at least 1 (dilation of a few blood vessels) were elicited bilaterally within 10 min. The lowest concentration that produced these symptoms in each subject was the optimal concentration of allergen solution in the CAC. Subjects who failed to show sufficient

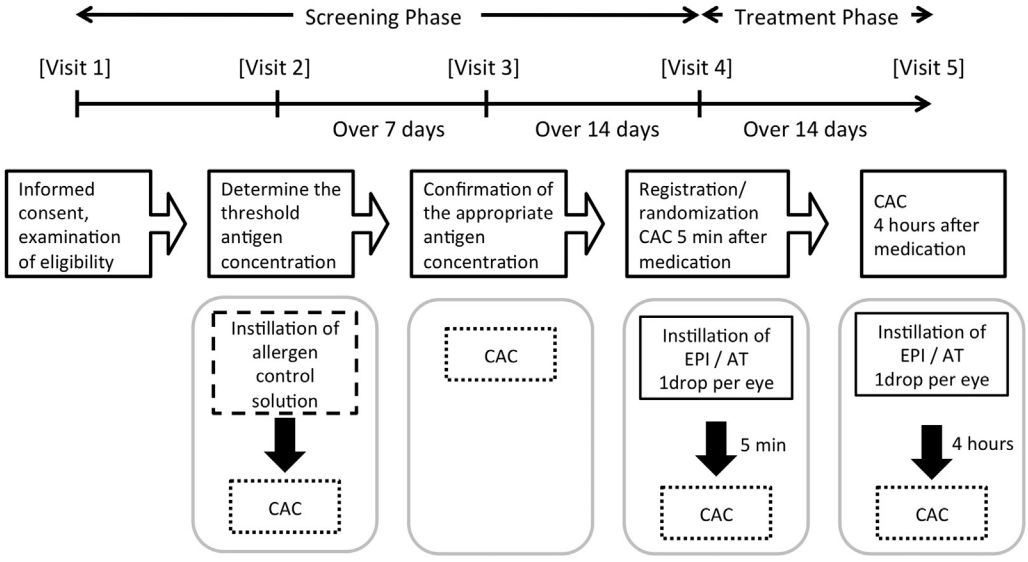

Fig. 1. Outline of this study. CAC, conjunctivitis allergen challenge; EPI/AT, epinastine hydrochloride ophthalmic solution 0.05% in one eye/artificial tear in the contralateral eye.