Ann Allergy Asthma Immunol xxx (2014) 1–6

Contents lists available at ScienceDirect

Efficacy of epinastine hydrochloride ophthalmic solution in allergic conjunctivitis by conjunctival cedar pollen allergen challenge

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ARTICLE INFO

Article history:
Received for publication October 1, 2013.
Received in revised form June 2, 2014.
Accepted for publication July 10, 2014.

ABSTRACT

Background: Epinastine hydrochloride is a selective histamine H_1 receptor antagonist that also inhibits IgE receptor-mediated histamine release from mast cells.
Objective: To show the superiority of epinastine 0.05% ophthalmic solution (epinastine) to placebo ophthalmic solution (placebo) and noninferiority to olopatadine 0.1% ophthalmic solution (olopatadine) for cedar pollen antigen-induced ocular itching and conjunctival hyperemia.
Methods: The study was conducted in ophthalmologically asymptomatic adult volunteers with seasonal allergic conjunctivitis using a conjunctival allergen challenge test. Subjects were randomized into 3 groups (n = 87) to evaluate superiority to placebo (visits 4 to 6) and 2 groups (n = 86) to evaluate noninferiority to olopatadine (visit 7). At each visit, a single administration of the study medication was instilled at 15 minutes (visit 4), 4 hours (visit 5), 8 hours (visit 6), and 4 hours (visit 7) before the conjunctival allergen challenge test. Ocular itching and conjunctival hyperemia of allergic conjunctivitis were assessed after the conjunctival allergen challenge test.
Results: For the primary end point, epinastine showed superiority to placebo for the inhibition of ocular itching and conjunctival hyperemia induced at 4 hours after the dose (equivalent to 4-times-daily dosing). For the secondary end points, epinastine significantly inhibited itching and conjunctival hyperemia induced at 15 minutes and 8 hours after the dose (equivalent to 2-times-daily dosing) compared with placebo. In addition, epinastine demonstrated noninferiority to olopatadine for ocular itching and conjunctival hyperemia. No adverse drug reactions or serious adverse events were reported throughout the study, indicating that epinastine has a good safety profile.
Conclusion: Epinastine is effective and safe for the treatment of allergic conjunctivitis.

Introduction

Seasonal allergic conjunctivitis is the most common allergic disease and affects millions of people worldwide. Regarding the underlying mechanism, degranulation of mast cells leads to the local release of inflammatory chemical mediators in the conjunctiva.[1] In this regard, the roles of mast cell stabilizers and H_1 blockers as topical therapeutic regimens have been extensively explored for the past 2 decades.

In general, environmental and conjunctival allergen challenge (CAC) studies are performed primarily for the clinical evaluation of antiallergic ophthalmic solutions. In environmental studies, the efficacy of antiallergic ophthalmic solutions has been evaluated in trials using natural exposure, such as during the pollen season. However, that model has an inherent drawback of different exposures between seasons and individuals.[2] Conversely, CAC studies use a defined exposure that can be adjusted for individuals with regard to the allergen exposure rate.[2–5] As models that allow for appropriate clinical assessment of allergic conjunctivitis, CAC studies have been used in the United States, Europe, Japan, and other countries.[6–8]

Epinastine hydrochloride is a topical ocular antihistamine that exhibits strong binding to histamine H_1 receptors and has potent anti-inflammatory properties resulting from the inhibition of the release of mediators, such as histamine and leukotriene, and the decrease of the downstream effects of leukotriene

Trial Registration: Clinicaltrials.gov identifier NCT01363700.
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Disclosure: Drs Fujishima, Ohashi, and Takamura have consulted for Santen Pharmaceutical Co Ltd.
Funding: This study was sponsored and funded by Santen Pharmaceutical Co Ltd, Osaka, Japan.

http://dx.doi.org/10.1016/j.anai.2014.07.007
1081-1206/

C_4, platelet-activating factor, serotonin, and other factors.[9–12] The authors conducted a phase III CAC study of epinastine hydrochloride 0.05% ophthalmic solution (epinastine) using an allergen solution of cedar pollen, the most widely dispersed pollen species in Japan.

Methods

Subjects

Adult volunteers with a history of seasonal allergic conjunctivitis and cedar pollen-specific IgE were selected. Subjects had to be asymptomatic, with no ocular itching or conjunctival hyperemia, before the allergen challenge. The main exclusion criteria included complications of extraocular or anterior ocular segment inflammatory disease or dry eye, a Schirmer test reaction no larger than 5 mm, recent (<90 days) intraocular surgery, or recent (<30 days) treatment for lacrimal punctum occlusion. Subjects using systemic corticosteroids within 28 days of screening or using antiallergic drugs, histamine H_1 receptor antagonists, or nonsteroidal anti-inflammatory drugs within 7 days before the screening phase were excluded. Topical application of any of these agents, except for areas of the head and face, was allowed. Hyposensitization therapy or immunomodulation therapy for allergic rhinitis or a similar condition and the need to wear contact lenses during the study period disqualified the subject from the study.

Allergen Solution

The authors used a Japanese cedar pollen allergen extract in 50% glycerol at 1:20 w/v (Torii Pharmaceutical Co Ltd, Tokyo, Japan). Before the challenge tests, the extract was diluted with a diluent of chondroitin sulfate 1:100 w/v and glycerol 2:100 w/v and then by 2-fold to final concentrations of 1:500, 1:1,000, 1:2,000, and 1:4,000 w/v. All diluted allergen solutions contained 2% glycerol.

Conjunctival Allergen Challenge

The allergen solution with the dilution ratio determined at the screening phase was instilled, and the severity of ocular itching in both eyes was assessed by the subject at 3, 5, and 10 minutes after the allergen challenge. Both eyes also were observed for conjunctival hyperemia at 5, 10, and 20 minutes after the allergen challenge.

Table 1 lists the criteria for scoring of ocular itching and conjunctival hyperemia. For efficacy evaluations regarding hyperemia, the summed total score of the bulbar and palpebral conjunctival hyperemia scores was used. In the inclusion criteria, only the bulbar hyperemia score was used.

Table 1
Scoring of ocular itching and conjunctival hyperemia

Score	Symptom
Itching	
0	none
1	intermittent itching
2	continuous itching
3	severe itching with desire to scratch
4	incapacitating itching with an irresistible urge to scratch
Palpebral conjunctival hyperemia	
0	none
1	dilation of several vessels
2	dilation of many vessels
3	impossible to distinguish individual blood vessels
Bulbar conjunctival hyperemia	
0	none
1	dilation of several vessels
2	dilation of many vessels
3	vasodilatation of all vessels

Efficacy and Safety Assessments

The primary end point was the ocular itching score and conjunctival hyperemia score at 3 specified time points after the allergen challenge (ocular itching at 3, 5, and 10 minutes; conjunctival hyperemia at 5, 10, and 20 minutes). The allergen challenge was conducted at 4 hours after instillation of the study drug for comparison with placebo. The secondary end points were the ocular itching score and conjunctival hyperemia score at specified times after the allergen challenge at visits other than the visit for the primary end point. Changes in the ocular itching score and conjunctival hyperemia score at 4 hours after dosing were selected as the primary end point because they correspond to 4-times-daily instillation, which is the indication for most antiallergic ophthalmic solutions in Japan.

Safety was evaluated based on adverse events, clinical laboratory test results, intraocular pressure measurements, and funduscopic findings.

Clinical Trial Design

Screening phase

This study was a single-center, double-masked, randomized comparison study (Fig 1) conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board of Kitasato University (Tokyo, Japan). The patients received oral and written information and provided informed consent.

At visit 1, subject eligibility was determined by performing tests such as serum allergen-specific IgE antibody measurements.

At visit 2, the threshold allergen concentration was determined. The subjects received topical instillations of the allergen solution, starting with 1 drop of extract (1:4,000 w/v) and increasing the dose by 2-fold every 10 minutes until ocular itching and bulbar conjunctival hyperemia with scores of at least 2 were observed. Subjects whose reactions after instillation of the 1:500 w/v extract did not meet these criteria were treated in accordance with “discontinuation during the observation period.”

At visit 3, the optimal threshold allergen concentration was verified. The authors confirmed whether the ocular itching and bulbar conjunctival hyperemia scores were at least 2 for at least 2 of the 3 time points in both eyes. If this was confirmed, visit 4 was scheduled for the subject.

Treatment phase

Epinastine vs placebo. At visits 4, 5, and 6, the superiority of epinastine to placebo was evaluated. Subjects were randomized into 3 groups (n = 87): group A (Epi/Pla), epinastine in one eye and placebo in the other eye; group B (Epi/Epi), epinastine in both eyes; and group C (Pla/Pla), placebo in both eyes. After instillation of the study drug, the allergen solution with the threshold concentration for each subject confirmed in the screening phase (visit 3) was instilled into both eyes at 15 minutes (visit 4; onset), 4 hours (visit 5; equivalent to 4-times-daily dosing), and 8 hours (visit 6; equivalent to 2-times-daily dosing).

Epinastine vs olopatadine. At visit 7, the noninferiority of epinastine to olopatadine was assessed. Subjects were randomized into 2 groups (n = 86): group D (Epi/Pla), epinastine in one eye and placebo in the other eye; and group E (Olo/Pla), olopatadine (Patanol; Alcon Japan, Ltd, Tokyo, Japan) in one eye and placebo in the other eye. The allergen solution was instilled 4 hours after dosing, and assessment was performed after the procedures described in the Conjunctival Allergen Challenge section.