



Allergic contact conjunctivitis and cross-reaction between phenylephrine and epinephrine due to phenylephrine eye drops

Phenylephrine is a sympathomimetic (α -adrenergic) drug used in eye drops to dilate the pupil to facilitate visualization of the retina and to treat nasal congestion and increased sinus pressure that result from rhinitis. Although sympathomimetic drugs are used often, allergic reactions are rare, especially when the drugs are administered systemically. Phenylephrine is responsible for most of the cases of allergic reactions to sympathomimetic reported in the literature.¹ Since the first description of contact dermatitis to phenylephrine in 1979, further cases have been described.^{2–8} We report a case of allergic contact conjunctivitis attributable to phenylephrine in eye drops, with cross-reaction between phenylephrine and epinephrine (adrenaline) confirmed by prick tests.

A 64-year-old woman with a history of hypertension and glaucoma, treated for several years with candesartan and phenylephrine eye drops (100 mg/mL) (containing as preservatives thimerosal and sodium bisulfite), was referred to our department after developing conjunctivitis attributable to the administration of phenylephrine eye drops 2 months before. She had avoided phenylephrine drops for 1 month, but later other eye drops with thimerosal as a preservative (diclofenac sodium and latanoprost eye drops) are tolerated.

The patch tests were removed after 48 hours, and readings were performed at 48 and 96 hours according to the recommendations of the European Contact Dermatitis Research Group. The European Standard series proved negative. We discarded the sensitivity to benzalkonium chloride after epicutaneous testing, added to the standard test containing thimerosal with negative results at 48, 72, and 96 hours. After 48 hours, the results of skin patch testing with phenylephrine eye drops were positive, so the patient was considered to be allergic to that substance. In addition, an oral challenge test was performed with up to 200 mg of sodium bisulfite with negative results.

Prick tests with phenylephrine, epinephrine, and other sympathomimetic agents produced positive results for phenylephrine (9 mm). Intradermal testing was performed for epinephrine and other sympathomimetic agents, with an immediate positive result for 1 mg/mL of epinephrine (containing sodium bisulfite as a preservative) at 1:10 dilution (20 mm) and phenylephrine eye drop at 1:10 dilution (18 mm). The eye drops were prepared in a hospital pharmacy and were free of the previous additives (thimerosal and sodium bisulfite) with the same concentration prepared in the original eye drops (100 mg/mL).

Ocular provocation testing was performed with phenylephrine. The concentration used for phenylephrine was 100 mg/mL, and later concentrations of 1/10 (10 mg/mL) and 1/100 (1 mg/mL) were prepared. For adrenaline, we started with 1 mg/mL and later with 1/10 and 1/100. We have not been able to prove what response threshold was the irritating one because our results were negative in the 10 controls (5 atopic and 5 nonatopic controls). There is evidence that nonirritating concentrations range from 25 100 mg/mL for the prick test and 1 to 0.25 mg/mL for the intradermal test.⁹ Within 3 hours, the patient developed eye itching, watery eyes, and conjunctival hyperemia. The symptoms disappeared 48 hours after treatment with oral dexchlorpheniramine and deflazacort.

Causes of allergic contact reactions of the eye region include topical medicaments, contact lens solutions, and eye cosmetics. Ophthalmic drugs contain a wide range of potential allergens. Phenylephrine is responsible for most of the cases in the literature.^{1–8}

The phenylamine family is divided into phenylpropanolamine-derived agents (ephedrine, pseudoephedrine, and norephedrine) and phenylethanolamine-derived agents (phenylephrine and

epinephrine). Cross-reactivity may exist among catecholamine derivatives, especially if the drug is administered systemically. However, little is known about the cross-reactivity patterns among the sympathomimetics that share a similar chemical structure.¹⁰

Some authors have reported several cases of ocular allergic dermatitis attributable to phenylephrine with tolerance of ephedrine in 2 of 3 patients and of pseudoephedrine in all 3 patients.⁸ Others describe 14 patients who developed ocular reactions attributable to phenylephrine, with cross-reactivity with pseudoephedrine in 80% of the cases and with ephedrine in 50%.¹⁰ It has been suggested that the central structure might be the sensitizing part of the drug.⁸

We do not find cross-reactivity between phenylephrine and phenylpropanolamine-derived agents. The differences in chemical structures might explain the absence of cross-reactivity, but we need further studies. We found cross-reactivity between phenylephrine and epinephrine. Both differ in terms of substitutions in the aromatic part of phenylethanolamine. Phenylephrine is an epinephrine analog that differs chemically from epinephrine by the absence of a hydroxyl group phenylephrine without any hydroxyl groups on the benzene ring.

Previous studies suggest late immunologic reactions (type IV), a combination of type I (IgE dependent) and type IV (in the case of this patient) reactions not found in the recent literature, and a mixed reactivity between phenylephrine and epinephrine. The period of latency between one kind of response and another makes us think that different contact velocities could exist among the antigens involved because of delayed absorption of the ocular mucous membrane and the period of latency with the T lymphocyte or the different kind of response in relation to the sensitivity of this patient.

To our knowledge, this is the first case of cross-reactivity between phenylephrine and epinephrine, with negative results to phenylpropanolamine-derived agents, confirmed by prick tests. The cutaneous test and provocation test are useful tools for the diagnosis.

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Efficacy and safety of an eye wash solution in allergic conjunctivitis after conjunctival allergen challenge



Cedar pollen is a major allergen for seasonal allergic conjunctivitis in Japan.^{1,2} A commercial eye wash in Japan (Eyebon Eye Wash; Kobayashi Pharmaceutical Co Ltd, Osaka, Japan) is a solution for washing away the pollen and allergic mediators from the ocular surface.³ It has anti-inflammatory agents (ϵ -aminocaproic acid, dipotassium glycyrrhizate), a tear replacement agent (chondroitin sulfate sodium), and an antihistaminic agent (chlorpheniramine maleate).

In this study (UMIN Identifier: UMIN000021320), we recruited 15 volunteers (11 men and 4 women; mean age, 30.6 years) with seasonal allergic conjunctivitis and positive test results for cedar pollen specific IgE in this prospective, randomized, single-center, 1-day, open-label, contralateral-controlled, double-blind, masked study to examine the efficacy and safety of the eye wash. This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Ethics at Kitasato University (Tokyo, Japan). Unwashed opposite eyes of the same individuals served as controls. A conjunctival allergen challenge (CAC) was performed bilaterally with Japanese cedar pollen (serially diluted in buffered saline and administered via a micropipette).^{2,4,5} One drop of a solubilized allergen was instilled into the conjunctival cul-de-sac. If the patient failed to react within a mean (SD) of 10 (1) minutes, increasingly concentrated doses were instilled at 10-minute intervals until a positive reaction was elicited. A positive CAC result was defined as an itching score greater than 2 and a hyperemia score greater than 2 in the conjunctival vessel bed in both eyes within a mean (SD) of 10 (1) minutes of receiving the patient's last dose of allergen. Any patient who failed to test positively was excluded from the study. A trained study technician observed the applications of the eye wash in the assigned eye at a mean (SD) of 5 (2) minutes from the time of the patient's qualifying for the challenge examination. First, we wiped the eyelashes and the eyelid skin with a wet tissue to prevent any contamination of the ocular surface by the skin lipids and the dermal flora. Second, we rinsed the eye with the solution for 10 seconds. Qualifying challenge was defined as a positive bilateral CAC reaction (≥ 2.0

itching and ≥ 2 hyperemia in the conjunctival vessel bed) within 10 minutes of instillation of the last titration of allergen.

Patients who had a known hypersensitivity to the eye wash, pregnant or nursing women, those with other ocular or systemic diseases, those undergoing any ocular surgical intervention within 3 months before the initiation of this study, and patients taking systemic medications were excluded. Safety measures before and after the study were assessed by the presence of adverse events and examinations of best-corrected visual acuity, slitlamp biomicroscopy, fundus photography, systolic and diastolic blood pressure, pulse rate, and cardiac auscultation. Primary (itching, redness) and secondary efficacy measures (eyelid swelling, chemosis) were evaluated by a numerical rating for each eye. Itching was scored from 0 to 4 points (0, none; 1, intermittent; 2, continuous; 3, severe itching; and 4, incapacitating itching). The other efficacy measures were scored from 0 to 4 points (0, none; 1, mild; 2, moderate; 3, severe; and 4, extremely severe). All symptoms were assessed at baseline (10 [1] minutes after the qualifying CAC test) and at a mean (SD) of 1 (15 seconds), 5 (1), 10 (2), 15 (3), 20 (5), 30 (5), 45 (5), and 60 (5) minutes after application of the eye wash. A paired *t* test was performed for statistical analysis using Microsoft Office Excel 2013 for Windows (Microsoft Corporation, Redmond, Washington). We compared the time-wise differences of mean redness, eyelid swelling, and chemosis scores from 1 to 60 minutes.

The results are given in Table 1. In summary, eyes treated with the wash had significantly lesser ocular itching scores than no treatment eyes, during 1 to 20 minutes ($P < .05$). Wash-treated eyes also had lower conjunctival redness scores than untreated eyes at 10 minutes and 30 minutes after treatment ($P < .05$). Wash-treated eyes had significantly lesser swelling scores than the untreated eyes between 5 and 15 minutes ($P < .05$).

No significant differences were found between wash-treated and untreated eyes in relation to chemosis scores ($P > .05$). No adverse reactions were observed in this study. A total of 93% of patients were satisfied with the ability of the eye wash to relieve the signs and symptoms.

In the current study, we used a CAC test with Japanese cedar pollen to test the effect of eye wash treatment on symptoms of allergic conjunctivitis. The eye wash solution contained anti-inflammatory agents, such as ϵ -aminocaproic acid and dipotassium glycyrrhizate, and corneal protective and antihistamine agents, including chondroitin sulfate sodium and chlorpheniramine maleate.

The eye wash treatment provided prompt and significant improvement of ocular itching scores after treatment. Eye wash treatment also provided significant relief of eyelid swelling as early as 5 minutes after treatment until 15 minutes. The ocular allergic response has both an early- and a late-phase reaction. The early-phase reaction is mainly caused by histamine.⁶ The early reaction results in

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