

Allergic contact reactions due to phenylephrine hydrochloride in eyedrops

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Background: Dermatitis of and around the eye is common. Allergic contact reactions from phenylephrine are rare despite extensive use by ophthalmologists. Previous reports do not indicate crossreactivity between phenylephrine and other sympathomimetic drugs in patch testing.

Methods: We report three cases of allergic contact reactions (dermato-conjunctivitis) after eyedrops. Skin prick tests, epicutaneous testing with the implicated drugs, additives, and a complete patch test battery, TRUE test (Upjohn-Pharmacia, Sweden), were performed in each patient.

Results: All skin prick tests were negative. The three patients showed positive patch tests to phenylephrine and one of them also to ephedrine. Tolerance of the other eyedrops without phenylephrine was verified by challenge.

Conclusion: Phenylephrine was the responsible agent for the reactions in our patients as confirmed by clinical findings and positive patch tests. Our findings suggest the central structure as the sensitizing part of drug in the second patient. Patch testing is essential for diagnosis of allergic contact reactions of and around the eye.

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INTRODUCTION

Phenylephrine is a sympathomimetic agent with effects on α -adrenergic receptors. This drug is frequently used in ophthalmology, in topical preparations for its vasoconstrictor and mydriatic properties. The most frequent side effects of phenylephrine hydrochloride in eyedrops are blurred vision, burning or stinging, tearing, conjunctival irritation, liberation of iris pigment into the anterior chamber and corneal edema.¹ Systemic reactions, mainly hypertensive crisis, are much less frequent.^{2,3} Phenylephrine hydrochloride is also employed in otic topical preparations to achieve decongestant effects, and in some rectal and vascular ointments.

In these preparations phenylephrine hydrochloride is a rather rare but well-known sensitizing drug.⁴⁻¹¹ Many topical ophthalmic drugs can sensitize,

and patch testing is essential for the accurate diagnosis of these adverse reactions.¹²

We report three cases of allergic contact dermato-conjunctivitis due to phenylephrine hydrochloride in eyedrops. Patch testing with other sympathomimetic α -adrenergic drugs was performed to identify cross reactivity.

CASES REPORTS

Case 1

A 73-year-old diabetic woman received two kinds of eyedrops: Colircusi Fenilefrina (FarmaCusi Laboratory, Spain) containing thimerosal, phenylephrine hydrochloride, sodium phosphate, sodium sulfite, and water; and Colircusi Tropicamida (FarmaCusi Laboratory, Spain) with tropicamide, benzalkonium chloride, hydrochloric acid, di-sodium edetate, sodium chloride, and water. Sixty minutes after application she developed eyelid erythema, ocular itching, conjunctival hyperemia, tearing, and photophobia. She was referred to our outpatient clinic by the ophthalmologist in the emergency

room. Oral antihistaminics and topical ophthalmic corticosteroids had been administered to treat the reaction, but the symptoms increased to a maximum in 12 to 24 hours with marked eczema around the eye and kerato-conjunctivitis. Next, oral corticosteroids were added to the treatment and total resolution was observed within 2 weeks.

Case 2

A 75-year-old woman received the same eyedrops as the previous patient. She presented with conjunctival hyperemia, eyelid erythema, photophobia, and ocular pruritus four to eight hours after application. The intensity of the symptoms increased to a maximum after 24 hours.

The reaction resolved over a few days with a topical ophthalmic corticosteroid.

Case 3

A 75-year-old man with chronic glaucoma received Ciclopléjico Colirio (FarmaCusi Laboratory, Spain) containing ciclopentolatum chloride, methyl and propyl *p*-hydroxy-benzoat, and sodium chloride; Colircusi Fenilefrina (as previously described), and Colircusi Anestesico (FarmaCusi Laboratory, Spain) containing tetracaine chloride, nafazoline, and water. He suffered marked eyelid edema, conjunctival hyperemia, photophobia, and ocular itching 12 to 24 hours after the application. This reaction resolved with topical ophthalmic corticosteroids within five days.

The three patients had previously used these topical ophthalmic drugs. All had occasionally experienced mild itching with some eyedrops, but they could not remember the names of these commercial preparations.

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ALLERGY TESTS

Skin prick tests were performed on the forearm of each patient with the implicated commercial preparations and pure drugs. We considered patch testing necessary for diagnosis.

Patch testing or epicutaneous testing is the diagnostic technique of applying a specific substance to the skin with the intention of producing a small area of allergic contact dermatitis. Generally, the back is used for patch testing. The test materials are applied in rows directly on the skin or covered with a small gauze flat. International contact dermatitis research groups have adopted a device that is a cellulose disc attached to a polyethylene-coated aluminum backing. An alternative method is a round aluminum chamber with the advantage that more patches can be applied. After 48 hours, the patches are removed and after a wait of 30 to 60 minutes the reactions are read. All test sites are reexamined routinely at 72 hours. The reading is directed to the center of the patch where the skin was not in contact with the tape.

Epicutaneous testing with the implicated commercial drugs and preservatives, and complete patch test battery TRUE-Test (Upjohn-Pharmacia, Sweden) were performed in our patients. When a commercial preparation gave a positive patch test, all compounds were individually tested. If intense positive results were still observed at 72 hours, a reading at 96 hours was also done.

RESULTS

All skin prick tests were negative.

Results of epicutaneous patch tests are shown in Table 1. Patch testing with available commercial preparations containing phenylephrine hydrochloride was positive in all patients. Patch testing with phenylephrine hydrochloride was positive in all patients. In patient 2, patch tests with ephedrine were also positive. The patch tests with involved preservatives, and other drugs contained in commercial preparations and TRUE test battery (Upjohn Pharmacia, Sweden) were negative in all patients. The patch tests with posi-

tive responses were also tested in ten atopic patients and ten normal persons as control and yielded with negative responses.

Conjunctival challenge with phenylephrine hydrochloride was not carried out because the clinical symptoms and the positive patch tests demonstrated that phenylephrine hydrochloride was the causative agent. Tolerance of the other implicated drugs in eyedrops without phenylephrine hydrochloride was verified by challenge.

DISCUSSION

Phenylephrine hydrochloride was the agent responsible for the reactions in our patients as confirmed by clinical findings and patch test data. All patients had previously used this drug. The symptoms began quickly and had maximal intensity between 12 and 24 hours after eyedrop administration. These facts and results of patch testing are consistent with a type IV hypersensitivity mechanism. In contact dermatitis, the specifically sensitized CD4 T helper cells provide the immunologic

Table 1. Results of Patch Testing

	Case 1			Case 2			Case 3		
	48 h	72 h	96 h	48 h	72 h	96 h	48 h	72 h	96 h
Thimerosal in petrolatum 1%	—	—	—	—	—	—	—	—	—
Preservatives of Colircusi Fenilefrina	—	—	—	—	—	—	—	—	—
TRUE-test	—	—	—	—	—	—	—	—	—
Colircusi Fenilefrina (as it is: commercial preparation)	+++	+++	+++	++	+++	+++	+++	+++	+++
Colircusi Tropicamida (as it is: commercial preparation)	—	—	—	—	—	—	ND†	ND	ND
Colircusi Anestésico (as it is: commercial preparation)	ND	ND	ND	ND	ND	ND	—	—	—
Ciclopéjico Colirio (as it is: commercial preparation)	ND	ND	ND	ND	ND	ND	—	—	—
Phenylephrine 1% aqueous	++	+++	+++	+	++	++	+	+	++
Phenylephrine 10% aqueous	+++	+++	+++	+++	+++	+++	+	++	+++
Phenylephrine in petrolatum 1%	++	+++	+++	—	+	+	+	+	+
Phenylephrine in petrolatum 10%	+++	+++	+++	++	++	+++	+++	+++	+++
Ephedrine in DMSO 10%	—	—	—	+	+	++	—	—	—
Ephedrine in DMSO 20%	—	—	—	+	++	++	—	—	—
Ephedrine in petrolatum 10%	—	—	—	—	—	—	—	—	—
Ephedrine in petrolatum 20%	—	—	—	—	—	—	—	—	—
Pseudoephedrine in petrolatum 10%	—	—	—	—	—	—	—	—	—
Pseudoephedrine in petrolatum 20%	—	—	—	—	—	—	—	—	—
Epinephrine in petrolatum 10%	—	—	—	—	—	—	—	—	—

† DMSO: dimethylsulfoxide

‡ ND: Not done

Table 2. Suggested Ophthalmic Tray¹²

Compound	Patch Test (%) Concentration	Vehicle*
Preservatives		
Benzalkonium chloride	0.1	aq
Benzethonium chloride	1	aq
Chlorhexidine gluconate	1	aq
Cetalkonium chloride	0.1	aq
Sodium EDTA	1	aq
Sorbic acid	2.5	pet
Thimerosal	0.1; 1	pet
β -adrenergic blocking agents		
Befunolol	1	aq
Levobunolol HCl	1	aq
Metipranolol	2	aq
Metoprolol	3	aq
Timolol	0.5	aq
Mydriatics		
Atropine sulfate	1	aq
Epinephrine HCl	1	aq
Phenylephrine HCl	10	aq
Scopolamine hydrobromide	0.25	aq
Antibiotics		
Bacitracin	5	pet
Chloramphenicol	5	pet
Gentamycin sulfate	20	pet
Kanamycin	10	pet
Neomycin sulfate	20	pet
Polymyxin B sulfate	20	pet
Antiviral drugs		
Idoxuridine	1	pet
Trifluridine	5	pet
Antihistaminics or antiallergic drug		
Chlorpheniramine maleate	5	pet
Sodium cromoglycate	2	aq
Anesthetics		
Benzocaine	5	pet
Procaine	5	aq
Oxyburprocaine	0.5	aq
Proxymetacaine	0.5	aq
Enzymatic cleaners		
Papaine	1	pet
Tegobetaine	1	aq
Miotics		
Pilocarpine	1	aq
Tolazoline	10	aq
Echothiopate iodine	1	aq
Other		
Epsilon aminocaproic acid	1	aq

* aq = aqueous and pet = petrolatum.

memory that accounts for the more rapid and intense response that occurs after reexposure to the contact allergen.¹³

The findings that excluded the possibility of an irritant contact dermatitis and confirmed an allergic mechanism in our

patients were (1) all controls had negative patch tests; (2) our cases showed a dose-response in positive patch tests, which was exemplified by stronger reactions with higher concentrations of the drug in the patch tests; and (3) the reaction persisted several days.

Since the first description of allergic contact dermatitis from phenylephrine in 1979, further cases have been described; however, it seems to be a rare condition despite extensive use by ophthalmologists.

We assessed possible crossreactivity with other sympathomimetic drugs in patch testing. Ephedrine and pseudoephedrine are derived from a phenylpropanolamine skeleton, while phenylephrine and epinephrine are derived from phenylethanolamine and differ by substitutions on the aromatic part of the molecule.

The very close chemical structures of ephedrine and pseudoephedrine could explain potential crossreactions between them.^{14,15} Previous reports, however, do not indicate crossreactivity between these drugs and epinephrine or phenylephrine, or between these two drugs.^{6,11} One of our patients had positive patch tests to phenylephrine and also to ephedrine. This finding suggests the central structure as the sensitizing part of the drug in this patient. On the other hand, the other two patients, and the cases reported elsewhere might be sensitized specifically to phenylephrine. Since her ocular reaction occurred, patient 2 had not received any oral drug containing sympathomimetics drugs. After the results of patch testing, we forbade them. The two other patients tolerated decongestant drugs containing sympathomimetics without problems after their ocular reactions.

Dermatitis of and around the eye is common. It can be endogenous or exogenous as consequence of allergic reactions. Cosmetics, topical ophthalmic drugs or the use of contact lens solutions can be involved.

Skin prick testing is not sufficient to diagnose allergic dermatitis of the eye because most cases are caused by a delayed hypersensitivity mechanism. Patch testing is essential for diagnosis.

Preservatives,¹⁶⁻²⁰ β -adrenergic blocking agents,^{21,22} mydriatics,^{4-9,11,23-25} antibiotics,^{16,26,19} antiviral drugs,^{27,28} antihistaminics,²⁹ and antiallergic,³⁰ anesthetics,^{16,19} enzymatic cleaners,^{18,31} and other single drugs^{4,32,33} have been impli-

cated in contact allergic reactions due to ophthalmic treatments.

Based on qualitative interpretation of literature an ophthalmic tray (Table 2) has been proposed to be used in patients with suspected contact allergy caused by locally applied ophthalmic drugs or the use of contact lens solutions.¹²

In our patients, the drugs involved in the reaction were known. A battery of contact allergens and an ophthalmic patch testing tray should be used for those reactions where the involved agents are unknown.

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