Case in Point

Allergic Reaction to Phenylephrine

Bonnie Vu, OD; Arthur Wong, OD; and Susannah Marcus-Freeman, OD

A patient's allergic reaction to phenylephrine resulted in bilateral keratoconjunctivitis.

Phenylephrine, a sympathomimetic drug, is commonly used in eye exams to dilate the pupil of the eye and to differentiate scleritis from episcleritis. Common adverse effects (AEs) of phenylephrine include subjective burning, stinging with lacrimation, rebound hyperemia, and liberation of iris pigment into the anterior chamber. Less common, systemic AEs include tachycardia and elevation of systemic blood pressure. Although instances of allergic reactions are rare, phenylephrine has been reported to cause contact dermatitis, blepharoconjunctivitis, and as in this case, keratoconjunctivitis.

CASE REPORT

An 83-year-old white male presented for a red eye evaluation 2 days after having undergone a comprehensive eye exam with dilation at the Malcom Randall VAMC clinic in Gainesville, Florida. The patient reported onset of blurred vision, which he described as looking through a fog. He further compared the feeling to pins sticking in his eyes. The patient noted he had experienced similar symptoms on a few other occasions following eye exams. At the most recent eye exam, proparacaine and fluorescein had been used for tonometry, and phenylephrine 2.5% and tropicamide 0.5% had been used for pupillary dilation.

The patient's best-corrected visual acuity was counting fingers at 2 feet in the right eye (OD) and left eye (OS). The best-corrected visual acuity 2 days prior had been 20/20 OD and OS. Pupils and extraocular motilities were unremarkable. Intraocular pressures were not obtained due to concern for a possible adverse reaction to proparacaine.

Slit-lamp evaluation revealed the lids to be lax, erythematous, and edematous in both eyes (Figure 1). A marked papillary reaction and 3+ bulbar conjunctival injection in both eyes (OU) also was evident. The corneas had 2+ filamentous strands with dense superficial punctate keratitis bilaterally (Figures 2a & 2b). Anterior chamber angles were open, but it was difficult to assess for cells and flare through the hazy corneas. Irides were flat and clear OU. Lens exam revealed modest nuclear sclerosis OU. Due to concern for allergic reaction to tropicamide or phenylephrine, the patient was not redilated. The level of vision loss was consistent with the degree of keratitis observed OU.

The initial diagnosis was acute chemical conjunctivitis most likely due to an AE to proparacaine. The plan was to start the patient on antibiotic eye drops qid OU, prednisolone qid OU, and artificial tears every hour OU. The patient was scheduled to return to clinic 4 days later for an anterior segment follow-up.

At the follow-up visit, the patient reported significant visual improvement. His best-corrected visual acuity was 20/40-2 without improvement on pinhole OD and 20/50-2 with improvement to 20/30+ on pinhole OS. Slit-lamp evaluation revealed 1+ bulbar conjunctival injection OU, intact corneal epithelium OU, and no cells or flare in the anterior chambers OU. Due to improving punctate epitheliopathy, the frequency of the antibiotic drops, the prednisolone, and the artificial tears was reduced to bid. After 3 days, he was instructed to discontinue them. The patient was scheduled to return in 2 weeks for an anterior segment follow-up.

At the next follow-up visit, the patient reported that his vision had returned to normal, and he had no further ocular AEs. His best-corrected visual acuity was 20/20-2 OD and 20/20 OS. Slit-lamp evaluation revealed mild blepharitis OU, trace bulbar conjunctival injection OU, and complete resolution of the keratitis OU. The assessment was acute allergic conjunctivitis thought to be secondary to an AE to proparacaine OU, yet the need to rule out hypersensitivity to tropicamide and/or

Dr. Vu is an optometrist in Altamonte Springs, and **Dr. Wong** and **Dr. Marcus-Freeman** are optometrists at Malcom Randall VAMC in Gainesville; all in Florida.

Figure 1. Erythematous and Edematous Eyelid

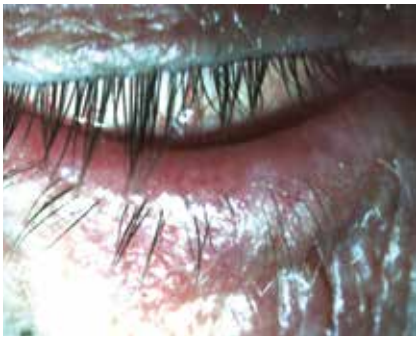
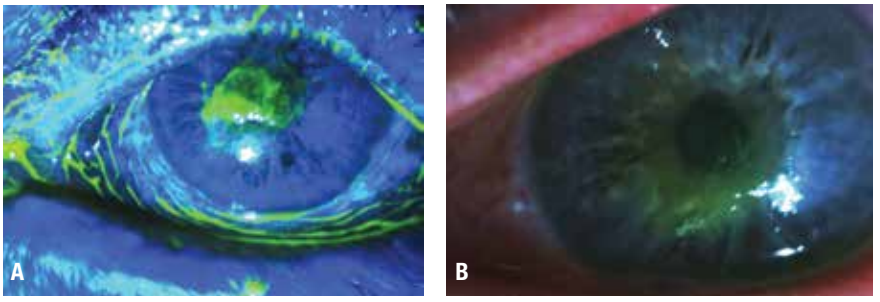


Figure 2. Grade 2+ Filamentous Strands With Dense Superficial Punctate Keratitis



A, Stained with fluorescein under cobalt blue light. B, With diffuse white light.

phenylephrine remained. The plan was to educate the patient of the possibility of allergic reaction on future visits and to recommend continued use of artificial tears as needed.

Through a careful and extensive chart review of all past visits, it was suspected that phenylephrine might be to blame rather than proparacaine. At the subsequent visit, the patient agreed to undergo testing to determine the culprit via instillation of proparacaine in one eye and tropicamide in the other. The patient had no reaction to either drop (checked 45 minutes after instillation and the following day). By process of elimination, phenylephrine was determined to be the offending agent.

DISCUSSION

Following a thorough review of the patient's chart, it was found that on other occasions he had presented with suspected allergic reactions following routine eye examinations. The patient reported he had experienced a reaction in 2007 but could not recall what drops were instilled in his eyes at the time. In addition, there was no documentation in his medical record of the subsequent reaction following that visit. Another reaction occurred in July 2010 with instillation of tropicamide 1%, phenylephrine 2.5%, and Fluress (fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP). In October 2013, when tropicamide 0.5%, proparacaine, and fluorescein strips were instilled, there was no reaction. The next reaction occurred in October 2014, when tropicamide 0.5%, phenylephrine 2.5%, proparacaine, and fluorescein strips were instilled.

This careful review of past exam notes revealed that phenylephrine and Fluress were the only drops that had not been instilled at the October 2013 visit when no AE was reported. However, Fluress was an unlikely culprit since it was not instilled in October 2014, and the patient still experienced an AE. Therefore, the agent most likely responsible for the allergic reaction in the patient, as confirmed by a review of the past notes and by the aforementioned pharmacologic test, was deemed to be phenylephrine (Table).

Adverse reactions to topical ocular medications and specifically to diagnostic eye drops have long been recognized. Mathias, Camarasa, Barber, Ducombs, and Monsálvez have reported on variations of conjunctivitis and periorbital erythema with positive patch testing to phenylephrine.[1-5] Geyer and colleagues reported on a study of 21 patients who had blepharoconjunctivitis after instillation of phenylephrine.[6] In this case study patient, severe keratoconjunctivitis was the clinical manifestation observed.

Villarreal and colleagues studied 31 patients who had a previous reaction to mydriatic drops. The study found that phenylephrine was the drug that most frequently caused an AE (93.5%).[7] One patient reacted to the preservative thimerosal, and 1 patient reacted to benoxiprocaine. Tropicamide was demonstrated to be very well tolerated as none of the patients tested positive on either the patch test or the pharmacologic test.

Tropicamide is a nonselective muscarinic antagonist commonly used for mydriasis due to its fast onset and short duration.[8] Adverse reactions to tropicamide are rare. Three studies reported on patients who had a positive patch test to tropicamide.[9-11] However, the reaction was not provoked by direct instillation of tropicamide into the eye.

Common in-office topical anesthetics, proparacaine, tetracaine, benoxinate, and lidocaine also can cause AEs. Corneal toxicity is a well-known complication with topical anesthetic abuse, whereas allergic reactions are considered rare. The most common symptoms include stinging

Table. Drops Used at Each Exam and Whether a Resultant Reaction Occurred

Exam	Tropicamide	Phenylephrine	Proparacaine	Fluorescein Strip	Fluress	Artificial Tears	Reaction
2007	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	x
July 2010	x	x			x		x
October 2013	x		x	x		x	
October 2014	x	x	x	x			x

and discomfort upon instillation. Common signs include punctate corneal epithelial erosions resulting indirectly from a decrease in reflex tearing, infrequent blinking, and increased tear evaporation.[12] Topical anesthetics also inhibit the migration of corneal epithelial cells and cause direct damage to the cells that are present, leading to impaired healing and epithelial defects.[13]

Manifestations of allergic reaction to topical anesthetics can include conjunctival hyperemia and edema, edematous eyelids, and lacrimation. One published case described a 60-year-old woman who developed eczematous dermatitis of the eyelids after ophthalmic anesthetic drops were instilled prior to laser surgery. Patch testing showed a positive response to benzocaine 5%, proparacaine, and tetracaine 0.5%.[14]

Preservatives, in general, can cause an allergic reaction. Benzalkonium chloride's (BAK) cytotoxic sequelae include possible trabecular cell death in glaucoma patients, disruption of tear film stability (even at low concentrations), and immune-allergenic properties. One article reported BAK as one of the 30 most frequent allergens causing allergic periorbital dermatitis.[15] Benzalkonium chloride is used in most brands of phenylephrine. However, preservatives in this patient's case were ruled out as instigating agents since both phenylephrine and tropicamide contain the same preservative, BAK 0.01%, yet this patient did not develop a reaction to tropicamide when used without phenylephrine. Expired medications also were not considered to be a factor as none of the medications used on the patient were indeed expired (the Malcom Randall VAMC clinic maintains a strict policy of discarding medications 28 days after being opened).

Although uncommon, phenylephrine sometimes has been found to cause a type 4 hypersensitivity reaction, also known as cell-mediated or delayed-type hypersensitivity.[16] First, helper T cells secrete cytokines. Activation of cytokines recruits and activates cytotoxic T cells, monocytes, and macrophages, leading to inflammation of the surrounding tissue. Examples of cell-mediated hypersensitivity include reactions to the tuberculin skin test and to poison ivy.

Type 1 hypersensitivity reactions, also known as immediate or anaphylactic hypersensitivity reactions, are not triggered by phenylephrine. In this type of reaction, IgE binds to the mast cell on initial exposure to an allergen. On second exposure, the allergen binds to the IgE, causing the mast cell to release mediators of inflammation, triggering physiologic responses. Examples of this type of hypersensitivity include those seen with penicillin, bee stings, hay fever, bronchial asthma, and food allergies, for example, to shellfish.

A toxic reaction's mechanism differs from that of a type 4 hypersensitivity reaction. Toxic reactions occur due to direct cytotoxicity of a drug caused by a low or high pH and either hyper- or hypo-osmolarity. Toxicity can lead to corneal and conjunctival cell necrosis or induce apoptosis, stimulating inflammatory reactions. Clinically, toxic reactions will present with follicles, whereas allergic reactions will present with papillae.

The definitive diagnostic methods used to determine the allergic agent causing ocular or periocular AEs are patch testing and conjunctival challenge.[7] Mathias, Camarasa, Barber, Ducombs, and Monsálvez used patch testing to confirm phenylephrine as the allergic agent in their series of cases. Patch testing entails the application of a small amount of an allergic agent that is taped onto the skin. The allergic agent is confirmed if the patient has a dermal reaction, wherein the area patched will become erythematous. When patch testing is negative or inconclusive, a conjunctival challenge is performed by instillation of the suspected allergic agent into the eye with subsequent observation to determine whether a reaction occurs. The sequelae found in Villarreal's study included itching, lacrimation, edema, erythema, and sometimes blepharitis.[7]

A direct conjunctival challenge with the suspected culprit was not pursued in this patient's case due to the known severity of the potential resulting reaction. The authors instead chose an indirect method of determining the implicating agent and used the process of elimination to whittle down the most likely suspect. A challenge with the medications suspected not to be likely offenders was undertaken. This spared the patient a likely repeat of the AE he had just recovered from.

MANAGEMENT

Allergic reactions can resolve without medical intervention. The first step is to remove the allergen. For delayed hypersensitivity reactions, treatments may include topical decongestants, cool compresses, and corticosteroids.[8] The treatment for immediate hypersensitivity reaction differs from that of delayed hypersensitivity reaction in that antihistamines are used.[17,18]

This patient reported receiving no treatment for his ocular symptoms following eye examinations in the past, yet he experienced complete resolution after each AE. In this case, both a steroid and a prophylactic antibiotic to facilitate a more rapid improvement were used.

CONCLUSION

Although uncommon, cases of allergic reaction to phenylephrine can occur. The incidence of phenylephrine allergy is 0.6%.6 The case study patient presented with a severe keratoconjunctivitis following routine eye examination with an accompanying history of adverse ocular signs and symptoms following multiple past exams.

It is important for all eye care clinicians to realize that AEs to diagnostic eye drops are possible and can occur following the most routine of visits. Such reactions can be caused by dilating agents, anesthetics, or preservatives, and these may be allergic or toxic. Clinicians should take special care to identify the instigating agent, and if possible, to avoid using such agents on patients during future exams. Clinicians also should understand how best to manage iatrogenic AEs when they encounter them in order to restore a patient's visual function as quickly as possible. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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