



Current dilemmas and controversies in allergic contact dermatitis to ophthalmic medications

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Abstract Identifying contact allergens in ophthalmic medications can be a challenging and daunting experience. We summarize data on topical ophthalmic medications with the potential to cause periorbital contact dermatitis and allergic conjunctivitis, highlighting current dilemmas and controversies in this area. The following groups of allergens are reviewed: preservatives, antiglaucoma medications (prostaglandin analogues, β -blockers, carbonic anhydrase inhibitors, parasymphathomimetics, sympathomimetics), antiinflammatory medications (nonsteroidal antiinflammatory drugs, corticosteroids), antibiotics, antivirals, antiallergic medications (antihistamines, cromones), anaesthetics, mydriatics, and cycloplegics.

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Introduction

A great variety of topical medications are used in modern ophthalmology for diagnostic and therapeutic purposes. As with the application of other topical drugs, the use of ophthalmic medications may induce local and systemic adverse effects. One of the undesirable, although relatively rare, reactions to topically applied ophthalmic medications is contact inflammation of the skin (periocular dermatitis) or conjunctiva (conjunctivitis), or both.^{1–3} Isolating responsible allergens is complicated by the growing number of long-term users of ophthalmic medications, newly emerging therapeutics, cross-sensitivity, allergy to preservatives, polypharmacy, and lack of standardized patch or

prick tests in clinical ophthalmology. These factors, as well as newly identified allergens, have been highlighted in a number of contributions. Our review provides an update on our current state of knowledge in this field, summarizing the data gathered for the commonly used topical ophthalmic preparations.

Methods

PubMed, MEDLINE, and Cochrane databases were searched for contributions focusing on contact allergic reactions to eye medications, restricted to allergic conjunctivitis or periorbital dermatitis, or both. The search was limited to published works in the English language within the past decade. The most relevant of the contributions are cited.

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Part I: Contact hypersensitivity to preservatives

Preservatives are important chemical agents incorporated in various ophthalmic medications. They delay decomposition of active chemicals and prevent microbial contamination. However, preservatives may induce a number of adverse reactions, especially if medications are used frequently or long-term, or both. Although the active drug usually causes the hypersensitivity reaction, allergic reactions to different preservatives have been described.³

Benzalkonium chloride

Benzalkonium chloride (BAK) is a widely used preservative in ophthalmics, as well as in the manufacture of cosmetic and cleaning products. Cytotoxic effects, including trabecular cell death in glaucoma patients, disruption of tear film stability even at low concentrations, and immunoallergenic properties of BAK have been well described.^{3,4} BAK is thought by some authorities to be a moderately allergenic preservative, and in relation to allergic periorbital dermatitis, was reported in one article as one of the 30 most frequent allergens.³

Its significance in periocular dermatitis appears to be changing: BAK was found to be less frequently patch test-positive in patients with eyelid dermatitis in Germany between 1995 and 1999 than during the preceding 5-year interval.⁵ The latter may be explained by changes in clinicians' approach to suspected contact allergy and a growing habit to prescribe preservative-free ophthalmic medications.⁵ In contrast, not a single positive reaction to BAK was found among 62 patients affected by periorbital dermatitis who used topical ophthalmic medications or contact lens solutions.⁶ In the same report, however, the authors emphasized that the value of patch testing for contact allergy to ophthalmic solutions might be doubtful due to the lower threshold to allergy of thin eyelid skin previously affected by dermatitis compared with the thick and healthy skin of the back where patch testing is performed.⁶

Thimerosal

Thimerosal is one of the most highly allergenic preservatives, historically found mainly in solutions for soft contact lenses, but also as an ingredient in some ophthalmic medications.⁴ Contact hypersensitivity to this preservative has been studied in vivo in different animal models, demonstrating changes consistent with immune complex-mediated hypersensitivity.³ Thimerosal is considered to be the most common concomitant type IV sensitizer among patients with allergic contact periorbital dermatitis⁷; however, a positive patch test to thimerosal is frequently considered clinically irrelevant in dermatologic patients,

with the exception of those patients using ophthalmic products.^{4,7} A case series included 36 patients with allergic conjunctivitis (accompanied by contact dermatitis in 5 patients) due to drops or soft contact lens solutions that contain thimerosal.³ Patch testing to thimerosal was positive in all of the patients.⁴

Phenylmercuric salts

Phenylmercuric nitrates or acetates are also common preservatives in ophthalmic solutions.⁸ Similar to thimerosal, phenylmercuric acetate frequently induces a type IV hypersensitivity reaction in patients with periorbital dermatitis but has often been interpreted as clinically insignificant.⁷ There was a reported rise of positive patch test to phenylmercuric acetate between 1995 and 1999, accounting for this tendency through the change of concentration of the test preparation from 0.01% to 0.05% in petrolatum.⁵ The authors of this report remind us that this might have been due to an irritant reaction rather than to a true positive reaction.⁵

Sodium metabisulfite

Sodium metabisulfite rarely causes hypersensitivity reactions in ophthalmic patients. Cases of contact allergic responses have been described in the modern literature, including contact dermatitis in response to application of eye drops containing this agent as a preservative.

Chlorobutanol

Chlorobutanol is a very common ophthalmic preservative with antibacterial and antifungal properties.³ Although considered rare, ocular hypersensitivity to chlorobutanol was demonstrated with a positive conjunctival provocation test in a patient presenting with an allergic conjunctivitis to Colircusi Fluotest.⁹ Subsequent skin tests to this agent were negative.⁹

Preservative-free medications

Preservative-free preparations reduce the potential for allergic and toxic side effects. They also simplify the diagnostic workup of contact hypersensitivity response, providing a more rapid identification of the allergen and enabling a switch to another medication if necessary.

Currently, the availability of nonpreserved ophthalmic products is increasing, along with a growing tendency for physicians to prescribe preservative-free medications. Manufacturing of preservative-free ophthalmic solutions began with the introduction of single-dose units, which remain commonly used in clinical practice. High cost and handling difficulties in the elderly population encouraged the development of multidose bottles where, depending on the system, preservatives are absorbed on a special porous

membrane, or microbial contamination of the container is prevented by a valve system.

Part II: Contact hypersensitivity to active ingredients of ophthalmic medications

Antiglaucoma medications

Antiglaucoma medications comprise a vast group of ocular preparations. Most patients use these drugs for many years and frequently in combination, predisposing them to irritant and allergic skin and conjunctival reactions.

Prostaglandin analogues

Prostaglandin analogues are a relatively new class of ophthalmic medications currently used as a first-line antiglaucoma agent. Compared with the other groups of antiglaucoma drugs, prostaglandin analogues have minimal, if any, systemic effect and have very few local adverse effects. Published reports describing contact dermatitis to these medications are very scarce. A case of contact dermatitis and conjunctivitis with a positive patch test to latanoprost (Xalatan) has been reported.¹⁰ In addition, there is a report of another patient with contact hypersensitivity caused by latanoprost-containing eye drops but with good tolerance to bimatoprost eye drops. A study has demonstrated ocular allergy to prostaglandin analogues in 1.5% of patients.¹

β -Blockers

Although the prescribing rate of β -blockers in the treatment of glaucoma was greatly reduced with the introduction of prostaglandin analogues, these agents remain widely used, especially in combination with the latter. Topical β -blockers can induce a range of systemic and local adverse effects, including irritant and allergic skin reactions.

Contact dermatitis and conjunctival manifestations of ocular hypersensitivity to various β -blockers have been reported. Contact dermatitis has been observed with timolol, levobunolol, metipranolol, betaxolol, befunolol, and carteolol, as confirmed by positive patch testing results.^{2,4,5,10,11} Although false-negative patch test results are common, even with a strong history of hypersensitivity reaction or positive stop-restart provocation to β -blockers, it remains an important diagnostic tool for identifying a potential allergen.¹⁰ A positive skin reaction to β -blockers has been found in 12.9% of patients using antiglaucoma medications.² Aside from the reported cases of multiple sensitization (cosensitization),¹¹ reports of true cross-reactivity between β -blockers (befunolol and carteolol; levobunolol, timolol and carteolol) have been published.^{2,11}

Carbonic anhydrase inhibitors

Topical and systemic carbonic anhydrase inhibitors are sulfonamide agents used to reduce intraocular pressure.

Dorzolamide hydrochloride

Dorzolamide hydrochloride is a topically applied anti-glaucoma agent. Among rarely reported serious systemic cutaneous reactions to this medication, a number of case reports attributed contact periorbital dermatitis or conjunctivitis, or both, to this medication.^{4,11} One of the earliest published reports described patients with a clinically apparent contact hypersensitivity to dorzolamide (conjunctivitis, 4%; eyelid dermatitis, 3%; pruritus, 3%); however, the authors did not attempt to confirm a causative agent by patch testing.¹¹ Six published cases of contact dermatitis to dorzolamide have been confirmed by conventional or scarified patch test technique.¹⁰ False-negative testing was reported to dorzolamide using normal or large Finn Chambers, but a positive patch test was reported after pretreatment of the skin with sodium lauryl sulfate. One patient in the same study had a weak positive response to conventional as well as large Finn Chambers patch tests and a false-negative reaction after pretreatment with sodium lauryl sulfate.

Parasympathomimetics

Pilocarpine hydrochloride is a parasympathomimetic that is largely used to reduce intraocular pressure in angle closure glaucoma. To date, only 3 reports of contact dermatitis to pilocarpine (all confirmed by patch testing) have been published.¹¹

Sympathomimetics

Apraclonidine hydrochloride is an α -2 adrenergic agonist developed to lower intraocular pressure and minimize the systemic side effects associated with the use of its parent drug, clonidine hydrochloride. This medication is commonly used before yttrium aluminium garnet laser capsulotomy to prevent an intraocular pressure rise after the procedure as well as in combination with a patient's maximum tolerated medical therapy for glaucoma. Systemic and local adverse effects to topical apraclonidine are still very common; therefore, it is primarily used as a very short-term therapy. Current reviews summarizing reports of allergic contact dermatitis and conjunctivitis to ophthalmic solutions refer to at least 3 publications describing contact dermatitis and conjunctivitis to apraclonidine hydrochloride.^{4,10} One of the first reports attributed contact hypersensitivity to 1% apraclonidine hydrochloride in 48% of long-term users.¹⁰ A later report showed half the incidence of allergic reactions to this medication; however, 0.5% apraclonidine concentration was used in the test.¹²

Brimonidine tartrate is another α -2 adrenergic agonist used in the management of glaucoma. There are many reports of contact allergy to brimonidine.^{4,10,13} Earlier reports demonstrated between 4.8% and 9% occurrence of contact allergic reactions to this medication. A more recent studies reported ocular allergy in 17.6% of patients using brimonidine tartrate.¹³ A meta-analysis of randomized trials demonstrated that brimonidine is associated with a higher rate of allergy than timolol, a commonly used β -blocker.¹⁴

There is a 22.7% risk of an allergic reaction to brimonidine in patients with known allergy to apraclonidine. This was not considered a high risk, however, and the author advocated brimonidine tartrate as a safe alternative for patients previously diagnosed with contact allergy to apraclonidine.¹⁵

Antiinflammatory medications

Nonsteroidal antiinflammatory drugs

Case reports of skin hypersensitivity reactions to diclofenac and indomethacin have been described.⁴ Ketorolac is a modern nonsteroidal antiinflammatory drug (NSAID) that has been reported to cause ocular allergy at least twice.¹⁰

Corticosteroids

Although very rare, paradoxical contact allergic reactions to ophthalmic corticosteroid medications may still occur; however, the last published case of this unusual adverse reaction to these agents dates back to 1997.

Antimicrobials

Mild to life-threatening allergic reactions can result from topical antibiotic application. Aminoglycosides, sulfonamides, and polypeptides are listed among the most allergenic classes of topically applied antibiotics.⁴

Aminoglycosides

- *Tobramycin*: Tobramycin is a well-tolerated eye preparation, frequently used in combination with a steroid. Recent reviews describe the occurrence of an allergic contact hypersensitivity to tobramycin as rare, referring to only 3 case reports.⁴
- *Neomycin*: Similar to tobramycin, neomycin is frequently used in the treatment and prevention of various ocular or postoperative infections. Neomycin is a sensitizing agent that has been reported to cause contact dermatitis in approximately 4% of patients. One study found that a significantly higher proportion of patients with allergic periorbital dermatitis were sensitive to neomycin compared with the group of nonallergic periocular dermatitis.⁵
- *Gentamicin*: Topical gentamicin may cause a range of toxic effects on the ocular surface but rarely causes contact dermatitis.⁴ There are 6 cases with a positive patch test to gentamicin; however, the symptoms of ocular allergy “were not well defined.”¹⁶ Importantly, there are also case reports describing cross-reactivity between different aminoglycosides.⁴

Sulfonamides

Although recognized as being highly allergenic, topical sulfonamides are not discussed in detail in this review,

because they are rarely used at present, having been replaced by other more effective and safe antibacterial drugs.

Cephalosporins

Allergic reactions are very common in the penicillin antibiotics due to the structural similarities. They are rarely used topically, usually as specially prepared drops of cefazolin.

Vancomycin

Vancomycin is a highly effective antibiotic against gram-positive cocci and is usually reserved for serious infections. To date, only 1 case report of contact dermatitis with a positive patch test to this agent has been described.¹⁰

Chloramphenicol

This agent is widely used in the treatment of mild ocular infections and is available in the UK without prescription. The risk of allergy to this topical medication is often underestimated. At least 7 reports have described contact dermatitis to this antibiotic, and in 1 report, an anaphylactic reaction was diagnosed.¹⁶

Other antimicrobials

Despite a number of earlier reports, the recent literature does not contain published reports of allergic contact dermatitis or conjunctivitis, or both, to topically applied ophthalmic formulations of tetracyclines, macrolides, and fluoroquinolones. This might be explained, because in most cases when an allergic reaction to an ophthalmic agent is suspected, physicians simply switch to another medication without an allergy workup. Another potential reason is that only a limited number of cases of contact dermatitis to any drugs are published in peer-reviewed literature.

Antivirals

The most frequently used topical antiviral medication in the UK is acyclovir eye ointment. It is typically well-tolerated during its relatively short application period of 7 to 10 days. Contact dermatitis to acyclovir is uncommon,⁴ but punctate keratopathy with a positive patch test result to acyclovir has been reported in 3% of patients.

Antiallergic medications

Although designed to prevent and treat allergy, anti-allergic preparations can rarely induce contact hypersensitivity responses.

Antihistamines

There is a single case report where contact conjunctivitis and dermatitis, confirmed by a patch test, were diagnosed in a patient receiving pheniramine maleate for grass pollen

allergy.¹⁰ It is also believed that chronic use of topical antihistamine medications can cause drug-associated allergy.

Cromones

There are 2 reports of contact dermatitis to sodium cromoglycate eye drops, including a case of a compound effect with the preservative BAK, revealed by patch testing.⁴

Anesthetics

Topical anesthetics are a large group of potentially allergenic medications widely used in ophthalmology for diagnostic and treatment procedures. The most frequently locally applied anaesthetics, tetracaine, oxybuprocaine (benoxinate), and proparacaine have been reported to cause contact dermatitis or conjunctivitis, or both.^{4,10} Studies on cross-sensitivity did not find a cross reaction between tetracaine and proparacaine, benoxinate and tetracaine, or benoxinate and proparacaine. Cocaine hydrochloride is seldom used in ophthalmic practice due to its high toxicity. It is applied for a short time to nasal mucosa during dacryocystorhinostomy and is rarely used for the confirmation of Horner syndrome.

Mydriatics and cycloplegics

The largest number of case reports on contact sensitivity to these agents describe allergic responses to topical atropine sulphate and phenylephrine hydrochloride.⁴ Other frequently used preparations of this group—tropicamide and cyclopentolate—may also induce contact ocular hypersensitivity, although significantly less often than the previous 2 agents.¹⁶

Conclusions

Contact dermatitis to eye preparations is an unpleasant event in ophthalmic practice that can lead to poorer compliance and efficacy of treatment. Ophthalmic medications may be responsible for 20% of cases of allergic periocular dermatitis.⁷

Diagnostic work-up including the patch testing of affected patients is a challenge due to a lack of individual test substances and confounding causes of allergic or contact dermatitis such as cosmetic products or airborne allergens,

and drug vehicle. Many reviews advocate the necessity of standardizing and increasing sensitivity of patch testing in ophthalmology.¹⁰ More proactive and efficient identification of allergens would promote strategies with the potential to improve patient comfort, compliance, and health.

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