

CPD

Contact dermatitis to ophthalmic solutions

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Summary

Periorbital and eyelid dermatitis is a recalcitrant and often distressing condition. Allergic contact dermatitis to ophthalmic solutions is an important cause of periorbital and eyelid dermatitis. In this review article, we discuss the allergens involved, the difficulties in patch testing, and the recommended concentrations and vehicles for patch testing.

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is one of many forms of contact dermatitis. ACD is caused by a type IV (delayed) hypersensitivity reaction to an allergen that is in contact with the skin. The terms 'dermatitis' and 'eczema' are interchangeable, and clinically ACD may resemble atopic dermatitis (AD). However, there can be overlap of the clinical features of the two conditions, and thus clinical grounds alone are not sufficient for a diagnosis of ACD.¹

Periorbital and eyelid dermatitis

Periorbital and eyelid dermatitis is a multiaetiological disease, which is often difficult to treat, and causes considerable distress to patients.² Like the hands, the face takes up a relatively small percentage of body surface area, but has a disproportionately larger sensory area, corresponding to the post-central gyrus of the cerebral cortex. This, combined with the fact the face is exposed, contributes to the distress caused to patients with this condition.

A common cause of periorbital and eyelid dermatitis is ACD, followed by the nonallergic causes, including

AD, irritant contact dermatitis, rosacea, tinea faciei, dermatomyositis (heliotrope rash) and seborrhoeic dermatitis.^{2–4} Indeed, the existence of nonallergic dermatitis of the eyelids can predispose the eyelids to allergen penetration. The skin of the eyelids is particularly vulnerable to sensitization from allergens, as it is only 0.55 mm thick whereas the rest of the facial skin is 2.0 mm thick,⁵ thus ACD of the eyelids can be severe.

A lack of atopic history and the presence of a number of affected areas in the same anatomical region should suggest an allergic or irritant component. Onset following application of a product suggests irritation or ACD. However, the timing is variable and the condition may take years to appear, particularly as sensitization to a product may not be present at initial use. In clinical appearance, there is little to distinguish ACD from AD in the periorbital and eyelid region (when evaluating the skin alone) and indeed, both may coexist. In the conjunctiva, ACD is associated with conjunctival follicles and inferior corneal superficial punctate keratopathy, indicating toxicity. Periorbital and eyelid eczema may be associated with atopic keratoconjunctivitis with upper tarsal conjunctival macropapillae or 'cobblestones', and conjunctival scarring and symblepharon.

ACD to ophthalmic solutions may be associated with eye irritation and stinging upon instillation of the product. Conjunctival hyperaemia (redness) and follicular conjunctival inflammation can occur, typically in the inferior conjunctival fornices where the eye drops are instilled. When the ophthalmic medication is being instilled in only one eye, unilateral dermatitis and eye symptoms are strong clues to the diagnosis. Blockage of

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Table 1 Allergens identified during the review.^{15,17–24}

Allergen	Patch test concentration, %	Delivery vehicle
Preservatives		
Benzalkonium chloride	0.005–0.13	Aq.
	0.1	NP
Benzethonium chloride	0.1–1.0	Aq.
Chlorhexidine gluconate	1.0	70% ETOH
	1.0	Aq.
Cetalkonium chloride	0.01	Aq.
Phenylmercuric nitrate	0.05	Pet.
Sorbic acid	0.5–2.5	Pet.
Thiomersal	0.01	Aq.
	0.1	Pet.
	0.1	NP
Beta blockers		
Befunolol	1	Aq.
Levobunolol hydrochloride	0.5–2.0	Aq.
	0.1–10	Pet.
Metipranolol	2	Aq.
Metoprolol	3	Aq.
1-Pentbutolol sulfate	2	Aq.
Timolol	0.5	Aq.
Timolol maleate	0.25–5.0	Aq.
Betaxolol	1.0–5.0	Aq.
Carteolol	1.0–2.0	Aq.
	Eye drops	As is
Mydriatics		
Atropine sulfate	1.0–2.0	Aq.pet.
	0.0006–2.0	NP
Epinephrine hydrochloride	0.1–1.0	Aq.
D-epinephrine	1.0	Aq.
Dipivalyl epinephrine hydrochloride	0.5–1.0	Aq.
Homatropine	1.0	NP
Phenylephrine hydrochloride	1.0–10	Aq.pet.
	1.0–10	Aq.
	0.1–5.0	Pet.
	1.0	NP
Scopolamine hydrobromide	0.25	NP
Tropicamide	1.0	NP
Cyclopentolate hydrochloride	0.1–0.5	Aq.
Antibiotics		
Bacitracin	20	NP
Chloramphenicol	1.5–10	Pet.
Gentamicin sulfate	20	Pet.
Kanamycin	10	Pet.
Neomycin sulfate	1.0	Aq.
	20	Pet.
	20	NP
Polymyxin B sulfate	20	Pet.
	5.0	NP
Tobramycin sulfate	0.3–25	Pet.
Sodium colistomethate	1.0	Aq. pet.
	Eye drops	As is
Vancomycin	0.005–5.0	Aq.
Antivirals		
Idoxuridine	0.0.2–1.0	Pet.
	5.0	Dimet.

Table 1 (continued)

Allergen	Patch test concentration, %	Delivery vehicle
Trifluridine	5.0–10	Pet.
	1.0 eyedrops	As is
	Ointment	As is
Antihistaminics		
Chlorphenamine maleate	5.0	Pet.
Sodium chromaglycate	2.0	Aq.
Ketotifen fumarate	0.069	Aq.
Pheniramine maleate	1.0	Aq.
Anaesthetics		
Benzocaine	5.0	Pet.
	5.0	NP
Procaine	5.0	Aq.
Oxyburprocaine	0.4	NP
Proxymetacaine	0.5	Aq.
Tetracaine	1.0	Aq.
Proparacaine	0.5	Pet.
Enzymatic cleaners		
Papain	0.1	Aq.
	1.0	Pet.
Tegobetaine	1.0–2.0	Aq., pet.
Miscellaneous		
Epsilon aminocaproic acid	0.1–10	Aq.
Tolazoline	10	Aq.
Echothiophate iodine	0.25–5.0	Aq.
Amlexanox	1.0	Pet.
Interferon-β	Eye drops	As is
Rubidium iodide	1.0	Pet.
D-penicillamine	1.0–3.0	Aq.
Diclofenac	1.0–2.0	Pet.
Prednisolone	0.5	Aq.
Resorcinol	1.0	Pet.
Pirenoxone	Eye drops	As is
	0.005–1.0	Aq.
Sodium bisulfite	0.2–1.0	Aq.
	Eye drops	As is
Sodium metabisulfite	1.0	Aq.
Trometamol	0.05–1.0	Aq.
Apraclonidine	10	Aq.
	Eye drops	As is
	1% Eye drops	As is
Brimonidine	0.2% Eye drops	As is
N-acetyl cysteine	10	Aq.
Bismuth oxide	0.5–5.0	Pet.
	Ointment	As is
Parabens	3.0	Pet.
	Eye drops	As is
Pilocarpine nitrate	2.0	NP
Pilocarpine hydrochloride	4.0	NP
Pilocarpine chlorhydrate	4.0	Pet.
Dorzolamide	0.0001–10	Aq.
	0.05–15	Pet.
	40	NP
	2% Eye drops	As is
Latanoprost	Eye drops	As is

Aq., aqueous solution; dimet., dimethylacetamide; NP, not provided; pet., in petrolatum. 'As is' refers to an unrefined, commercially available product.

the lacrimal duct will mean that topical solutions are more likely to overspill onto the surrounding skin rather than drain. Conjunctival illnesses such as allergic conjunctivitis are likely to result in physical manipulation of the eyelids, thus further damaging the barrier function of the eyelid epidermis.

Ophthalmic solutions cover a wide variety of drug classes used to treat ocular diseases. Therefore, with the immune system of patients exposed to so many different molecular structures, it is to be expected that some may be recognized as allergens. In this review, we discuss the literature regarding ACD to ophthalmic solutions. We undertook to carry out a comprehensive summary of all data including delivery vehicles and dilutions to come up with a comprehensive list of known allergens, to systematically investigate this common clinical problem, and to identify the difficulties involved and techniques to tackle these.

Analysis of allergens

We performed a literature search in November 2010 using PubMed and MEDLINE with the search terms 'contact dermatitis' and 'ophthalmic solutions' combined, covering the period 1968–2010. Articles not in English were excluded.

In most cases, identification of allergens was via patch testing. In other cases, resolution of symptoms following discontinuation of the offending product was diagnostic. Where possible, we have given the concentrations of the allergens used and the vehicle in which the allergen was suspended or dissolved (Table 1).

We found only one report of a newer treatment for allergic conjunctivitis, olopatadine, causing ACD; this was implicated in periorbital ACD with some depigmentation.⁶ The report did not include formal patch testing, but the product was implicated on the grounds of history. It is difficult to comment on the relative frequency of contact dermatitis to the individual allergens, as they are not always tested together and much of the information gathered from individual case reports. Feser *et al.*² reported that the Erlangen data showed that thiomersal was the commonest allergen, followed by gentamicin, neomycin and phenylephrine.

Patch testing

Patch testing is the mainstay of diagnosis in ACD, and has a sensitivity of 70% and specificity of 80%.¹ Allergens are applied to the skin, and then removed 2 days later and the skin examined for a reaction. The

area is then read again at day 4 and sometimes day 7, as a reaction can take longer to emerge.

The thin skin on the eyelids provides diagnostic challenges when performing patch tests, as such tests are usually performed on the back, which has a considerably thicker epidermis. If the history is strongly suggestive, but the patch test is negative, a provocative use test (PUT) where the suspected allergen is re-introduced after withdrawal to see if symptoms recur, may be useful. Alternatively, tape stripping, scratching, or pretreatment of the skin with sodium lauryl sulfate can be used to damage the skin barrier and allow greater sensitivity of the patch test.^{7,8}

There may be difficulties in obtaining a meaningful patch-test result for certain allergens. Nino *et al.* reported the existence of cross-sensitization of the beta-blocker timolol in a patient using betaxolol, and outlined the difficulties with obtaining positive results with beta-blockers. Cross-sensitization between bufenolol and carteolol has also been reported.^{9,10} The similar chemical structures of beta-blockers has been proposed as the mechanism for these cross-reactions. Difficulties with obtaining positive results with mydriatics have also been described.¹¹ Chromoglycate was reported by Camarassa *et al.*¹² to be strongly linked with ACD in a patient's history, yet it yielded positive results only when co-applied with benzalkonium chloride. This could indicate that the immune system only recognizes the combination of the two molecules as an allergen. Difficulties with dorzolamide have also been reported by Kluger *et al.*,¹³ who found use of a repeated open application test (ROAT) to be more sensitive than conventional closed patch testing (although not as an alternative). The ROAT requires daily application of a suspected allergen to an area of normal skin without occlusion to elicit a response. In the case reported, a memory phenomenon (systemic contact dermatitis) was seen, in that application of the allergen to a different site caused recurrence of the previously experienced periorbital and eyelid dermatitis. A reverse systemic ACD has been reported by Akita *et al.*¹⁴; who found that in patients with positive patch tests to phenylephrine, there was a recurrence of the reaction at the patch test site after the suspected allergen (eyedrops) was re-introduced.

Because of the frequency of reactions to ophthalmic solutions, Herbst and Maibach¹⁵ initially proposed a standardized ophthalmic battery for patch testing, comprising 37 items identified in their first review covering a period of 21 years. In our review, we identified 74 items. Clearly, it is not practical to test

such a large number in every patient with periorbital or eyelid dermatitis.

Currently the standard battery used in our centre and most centres in the UK (variations on the British Society of Cutaneous Allergy Standard Series) contains (from this list of 74 items) only parabens mix 16% petrolatum (pet.), caine mix III 10% pet. (used to test for local anaesthetic) and sodium metabisulfite 1% pet. However, in facial eczema, a facial series is added, which in our centre also contains thiomersal, chlorhexidine digluconate, benzalkonium chloride and sorbic acid. Of these, only sorbic acid 2% pet. is on the British Society of Cutaneous Allergy (BSCA) facial series. In addition, if there is a strong suspicion of a topical agent being the cause, the BSCA medicament series may be appropriate, which contains chloramphenicol 5% pet., gentamicin sulfate 20% pet., bacitracin 5% pet., polymyxin B 5% pet., benzalkonium chloride 0.1% aq., chlorhexidine digluconate 0.5% aq., sorbic acid 2% pet., and sodium metabisulphite 1% pet. Our local battery also contains caine mix IV. Consensus is needed in justifying a new battery specifically for ophthalmic preparations. It may be more practical to expand the currently used medicament series, and include it in facial batteries when the eyes are involved.

The patient's history will therefore be the best director as to what preparations need to be patch tested. Efforts should be made to obtain the individual ingredients in addition to the whole product. In addition, if a strong history is suggestive, ROAT, PUT, and preparation of the skin by tape stripping, scratching or application of SLS should be used to increase sensitivity.

The possibility of ICD should also be considered, because of the fragility of the eyelid skin and accumulation of solution, particularly when there is blockage of the lacrimal duct.¹⁶ In these cases, switching to an alternative product is likely to have a similar effect. Spaeth recommended using a tissue wedged into the inner canthus of both eyes to absorb excess fluid in these circumstances.

Conclusions

Ophthalmic solutions are used for a large variety of conditions and therefore cover a wide class of chemicals. As more preparations are developed and used for the treatment of ocular disease, the provided list is likely to expand. Because of the detrimental effect of periorbital and eyelid dermatitis on a patient's quality of life, it is important to continue to report and review these reactions in the future.

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A personal tribute from Dr A. A. Mughal: I worked with Barry as his registrar early in my career and found him to be a supportive and encouraging tutor who was both patient and inspiring. He was a pioneer in the field of cutaneous allergy, and will be sorely missed by both the Dermatology community and all that knew him. Our thoughts are with his family at this difficult time.

Learning points

- ACD is a common cause of eyelid and periorbital dermatitis.
- Several lists of allergens have been reported.
- Patch tests may not be useful for ACD in the eye area, as the allergens are usually applied to the back, which has thicker skin.
- Crossreactions and reactions only to combinations make patch testing more difficult.
- We identified 74 possible causes for ophthalmic ACD.
- Few of these were found in the batteries in general use in the UK.
- The patient's history will be a major determinant of which substances should be used in tests for ophthalmic ACD.

References

- 1 Bourke J, Coulson I, English J. Guidelines for the management of contact dermatitis: an update. *Br J Dermatol* 2009; **160**: 946–54.
- 2 Feser A, Plaza T, Vogelsang L, Mahler V. Periorbital dermatitis – a recalcitrant disease: causes and differential diagnoses. *Br J Dermatol* 2008; **159**: 858–63.
- 3 Herbst RA, Uter W, Pirker C *et al.* Allergic and non-allergic periorbital dermatitis: patch test results of the Information Network of the Departments of Dermatology during a 5-year period. *Contact Dermatitis* 2004; **51**: 13–19.
- 4 Landeck L, Schalock PC, Baden LA, Gonzalez E. Periorbital contact sensitisation. *Am J Ophthalmol* 2010; **150**: 366–70.e2.
- 5 Reitschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. USA: Lippincott., Williams & Wilkins, 2001; 1, 1–4.

- 6 Suchi ST, Gupta MSA, Srinivasan MSR. Contact allergic dermatitis and periocular depigmentation after using olatidine eye drops. *Indian J Ophthalmol* 2008; **56**: 439–40.
- 7 Corazza M, Virgili A. Allergic contact dermatitis from ophthalmic products: can pre-treatment with sodium lauryl sulfate increase patch test sensitivity? *Contact Dermatitis* 2005; **52**: 239–41.
- 8 Corazza M, Masieri LT, Virgili A. Doubtful value of patch testing for suspected contact allergy to ophthalmic products. *Acta Derm Venerol* 2004; **85**: 70–1.
- 9 Nino M, Napolitano M, Scalvenzi M. Allergic contact dermatitis due to the β -blocker betaxolol in eye drops with cross-sensitivity to timolol. *Contact Dermatitis* 2010; **62**: 319–20.
- 10 Nino M, Suppa F, Ayala F, Balato N. Allergic contact dermatitis due to the β -blocker befunolol in eyedrops, with cross-sensitivity to carteolol. *Contact Dermatitis* 2001; **44**: 369.
- 11 Villarreal O. Reliability of diagnostic tests for contact allergy to mydriatic eyedrops. *Contact Dermatitis* 1998; **38**: 150–4.
- 12 Camarassa JG, Serra-Baldrich E, Monreal P, Soller J. Contact dermatitis from sodium chromoglycate containing eye drops. *Contact Dermatitis* 1997; **36**: 160–1.
- 13 Kluger N, Guillot B, Raison-Peyron N. Systemic contact dermatitis to dorzolamide eye drops. *Contact Dermatitis* 2008; **58**: 167–8.
- 14 Akita H, Akamatsu H, Matsunaga K. Allergic contact dermatitis due to phenylephrine hydrochloride, with an unusual patch test reaction. *Contact Dermatitis* 2003; **49**: 232–5.
- 15 Herbst RA, Maibach HL. Contact dermatitis caused by allergy to ophthalmic drugs and contact lens solutions. *Contact Dermatitis* 1991; **25**: 305–12.
- 16 Spaeth GL. Allergic contact dermatitis caused by topical eye drops. *Am J Ophthalmol* 2006; **142**: 706.
- 17 Herbst RA, Maibach RL. Contact dermatitis caused by allergy to ophthalmics: an update. *Contact Dermatitis* 1992; **27**: 335–6.
- 18 Herbst RA, Maibach RL. Allergic contact dermatitis from ophthalmics: update 1997. *Contact Dermatitis* 1997; **37**: 252–3.
- 19 Chaudhari PR, Maibach RL. Allergic contact dermatitis from ophthalmics: 2007. *Contact Dermatitis* 2007; **57**: 11–13.
- 20 Vilaplana J, Zaballos P, Romaguera C. Contact dermatitis by dipivefrine. *Contact Dermatitis* 2005; **52**: 169–70.
- 21 Hashimoto Y, Aragane Y, Kawada A. Allergic contact dermatitis due to levobunolol in an ophthalmic preparation. *J Dermatol* 2006; **33**: 507–9.
- 22 Erdman S, Hertl M, Merk HF. Contact dermatitis from levobunolol eyedrops. *Contact Dermatitis* 1999; **41**: P44–6.
- 23 Seitz CS, Brocker EB, Trautmann A. Eyelid dermatitis due to sodium metabisulfite. *Contact Dermatitis* 2006; **55**: 249–50.
- 24 Gonzalez-Mendiola MR, Balda AG, Delgado MC *et al*. Contact allergy from tobramycin eyedrops. *Allergy* 2005; **60**: 527–8.

CPD questions

Learning objective

To demonstrate an understanding of the up-to-date evidence relating to periorbital and eyelid dermatitis, including methods for investigating allergic causes and known allergens in ophthalmic solutions.

Question 1

What is the average thickness of the skin of the eyelid?

- a) 0.25 mm
- b) 0.55 mm
- c) 0.75 mm
- d) 2.00 mm
- e) 2.50 mm

Question 2

The skin of the back is thicker than both eyelid and facial skin. Which of the following methods have been used to increase the sensitivity of patch testing on the back?

- a) Adding soap to the test chamber allergen
- b) Intraepidermal pricking
- c) Pre-treatment with sodium chloride
- d) Tape-stripping of the skin
- e) Warming the skin with warm glass

Question 3

What is the sensitivity and specificity, respectively, of patch testing in the diagnosis of allergic contact dermatitis?

- a) 50% and 60%
- b) 60% and 50%
- c) 80% and 50%
- d) 70% and 80%
- e) 95% and 90%

Question 4

Which of the following ophthalmic sensitizers is on the British Society for Cutaneous Allergy facial series?

- a) Benzalkonium chloride
- b) Chloramphenicol
- c) Sodium metabisulfite
- d) Sorbic acid
- e) Thiomersal

Question 5

Which area of the brain corresponds to the primary sensory area of the cerebral cortex?

- a) Inferior temporal gyrus
- b) Superior temporal gyrus
- c) Pre-central gyrus
- d) Post-central gyrus
- e) Sylvian fissure

Instructions for answering questions

This learning activity is freely available online at <http://www.wileyhealthlearning.com/ced>.

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- Reflect on the article
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