Periorbital dermatitis as a side effect of topical dorzolamide

Y M Delaney, J F Salmon, F Mossa, B Gee, K Beehne, S Powell

Aim: To report periorbital dermatitis as a late side effect of topical dorzolamide hydrochloride (Trusopt), a drug used to reduce intraocular pressure.

Methods: A retrospective study of 14 patients who developed periorbital dermatitis while using topical dorzolamide hydrochloride was undertaken. Six patients underwent patch testing for sensitivity to Trusopt, dorzolamide hydrochloride, and the preservative benzalkonium chloride.

Results: The periorbital dermatitis occurred after a mean period of 20.4 weeks of commencing dorzolamide hydrochloride therapy. 13 patients had used preserved topical β-blocker treatment for a mean period of 34.2 months without complication before the introduction of dorzolamide. In eight (57.1%) the dermatitis resolved completely after discontinuing dorzolamide but in six (42.9%) resolution of the dermatitis did not occur until the concomitant preserved β-blocker was stopped and substituted with preservative free drops. Patch testing for sensitivity to Trusopt, dorzolamide hydrochloride, and benzalkonium chloride was negative.

Conclusion: These findings suggest that dorzolamide can cause severe periorbital dermatitis. Although the dermatitis may resolve when dorzolamide is discontinued, this does not always occur and in some patients all topical medication containing benzalkonium chloride needs to be stopped.

Topical dorzolamide hydrochloride (Trusopt; Merck & Co Inc, West Point, PA, USA) is a thienothio-pyrano-2-sulphonamide carbonic anhydrase inhibitor. It is formulated as an aqueous solution using standard ophthalmic components, including hydroxyethyl cellulose, and preserved with 0.0075% benzalkonium chloride. Compared to oral carbonic anhydrase inhibitors (CAI) a significantly lower incidence of systemic side effects occurs with topical application. However, local side effects such as stinging, tearing, blurred vision, photophobia, conjunctivitis, punctate epithelial keratitis, and corneal decompensation have been reported.

In this study, we present a series of 14 patients who developed moderate to severe periorbital dermatitis as a late side effect of topical dorzolamide. To our knowledge, only one previous case of this complication has been published.

METHODS
Between 1996 and 1998, 14 patients who developed periorbital dermatitis while on dorzolamide hydrochloride presented to the Oxford Eye Hospital (Figs 1 and 2). We retrospectively reviewed their clinical and photographic records. Age, sex, ophthalmic diagnosis, history, duration of topical medications, and history of previous allergy were recorded. Statistical analysis was undertaken using Fisher’s exact test and a p value of <0.05 was considered statistically significant.

All patients were contacted by letter to attend for patch testing at the dermatology department of the Churchill Hospital, Oxford and six patients accepted (see Table 1). Patch testing was carried out according to the International Contact Dermatitis Research Group (ICDRG) recommendations and was performed on average 16 months (range 5–43 months) after the dermatitis occurred. Using the Finn chamber method, six patients were tested to a standard series of allergens, to benzalkonium chloride 0.1% in water, to Trusopt, and to pure dorzolamide hydrochloride 1%, both in petrolatum and water. The duration of occlusion was 2 days and results were read at day 3 and day 5. These patients were also prick tested to Trusopt and results read at 15 minutes and 48 hours. Three patients later underwent patch testing to dorzolamide hydrochloride 5% applying one series to normal skin and another series to celiotape stripped skin, to aid penetration of dorzolamide through the epidermis.

RESULTS
The clinical findings of the 14 patients are summarised in Table 1. All 14 patients developed dermatitis while using topical dorzolamide treatment. This occurred a mean period of 20.4 weeks (range 4–40 weeks) after commencing therapy. At the
The dermatitis did not resolve until the concomitant topical benzalkonium chloride and no adverse conjunctival or lid hypersensitivity occurred and these patients are now maintained on preserved monotherapy (n=2) or preserved dual therapy (n=2) without complication.

**DISCUSSION**

Carbonic anhydrase inhibitors are related to the sulphonamide group of drugs which are known sensitizers, and ocular hypersensitivity reactions have been reported with dorzolamide which include conjunctivitis, eyelid oedema, and eyelid irritation.

In this series, the dermatitis occurred a mean period of 20.4 weeks (range 4–40 weeks) after commencing therapy with topical dorzolamide. Patients obtained their medication from different pharmacies throughout the Oxfordshire area, over an average period of 5 months, which discounts the possibility of a manufacturing error isolated to one particular batch of Trusopt as the cause of the dermatitis in these patients. In our unit dorzolamide is most often used as an adjuvant rather than as a primary therapy and 13 of the 14 patients had been on topical β blocker therapy for a mean period of 34.2 months without complication before dorzolamide was introduced. Topical β blockers have been used as first line hypotensive therapy in the medical management of glaucoma for more than 30 years and an extensive local side effect profile has been documented which includes blurring, irritation, corneal anaesthesia, and punctate keratitis. However, contact dermatitis is rarely associated with their use and in our literature search, using the Medline database, we found a total of 15 case reports of patients who developed contact allergy to topical timolol,

### Table 1

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age, sex</th>
<th>Diagnosis</th>
<th>Concomitant topical bb and duration of Rx (months)</th>
<th>Duration of Trusopt Rx (weeks)</th>
<th>Resolution after withdrawal of Trusopt</th>
<th>Previous adverse reaction to topical medication</th>
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<tbody>
<tr>
<td>1</td>
<td>77, M</td>
<td>POAG</td>
<td>Levobunolol (33)</td>
<td>20</td>
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<tr>
<td>2</td>
<td>84, F</td>
<td>POAG</td>
<td>Betaxolol (12)</td>
<td>20</td>
<td>Yes</td>
<td>Neomycin</td>
</tr>
<tr>
<td>3</td>
<td>75, F</td>
<td>HZO</td>
<td>Betaxolol (83)</td>
<td>28</td>
<td>Yes</td>
<td>Dipivefrin</td>
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<td>4</td>
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<td>PPF</td>
<td>Levobunolol (33)</td>
<td>8</td>
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<td>Dipivefrin</td>
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<tr>
<td>5</td>
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<td>POAG</td>
<td>Timolol (19)</td>
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<td>Chloramphenicol</td>
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<td>Timolol (45)</td>
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<td>POAG</td>
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<td>9</td>
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<tr>
<td>11</td>
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<td>4</td>
<td>Yes</td>
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<tr>
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<td>13</td>
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<td>14</td>
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<td>Levobunolol (15)</td>
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POAG = primary open angle glaucoma; HZO = herpes zoster ophthalmia; PPF = pseudoexfoliation; OHT = ocular hypertension; Rx = treatment; bb = β blocker.

* Patients who underwent patch testing; † the time recorded is the duration of β blocker therapy before the introduction of dorzolamide.
and dorzolamide hydrochloride 1% and 5%. In the previously reported case of allergic dermatitis caused by dorzolamide, strongly positive skin reactions to dorzolamide, down to a dilution of 0.5% aqueous and 1% petrolatum were recorded, thereby confirming a true contact allergy. Our methodology was identical to that used by Aalto-Korte and the reason for the repeatedly negative patch testing in our patients is not clear. False negative results following patch tests to commercial ophthalmic solutions are not infrequent and have been reported in the literature. In a review of the subject, also reported cases of allergic dermatitis caused by topical ophthalmic preparations which defied aetiological diagnosis, either because they represented false negative patch tests, or because irritation, rather than sensitisation, was involved. Some authors have therefore modified their technique by performing patch testing on stripped skin (as we did in three of our patients) or by increasing the size of the patch test area. Interestingly, in the two patients who were rechallenged with topical dorzolamide, the periorbital dermatitis recurred within 4 days, thus satisfying one of the criteria proposed by Naranjo et al to assess causality of adverse events by drugs.

In conclusion, this retrospective study suggests that dorzolamide can cause severe periorbital dermatitis in patients with glaucoma or ocular hypertension. While the dermatitis resolves after withdrawal of dorzolamide in most patients, in others a subsequent irritation to the preservative benzalkonium chloride occurs. Patients on dorzolamide should be warned of this potential late side effect.

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REFERENCES