Case Report

Allergy to Timolol Contained in Eyedrops for Glaucoma

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Abstract

Background: Allergic eyelid dermatitis is a common but often misdiagnosed disease that is related to eyedrops, topical cosmetics or skin care products. With regard to eyedrops, adverse reactions can be caused by both active ingredients and excipients. Identification and elimination of causative agents is the mainstay of management.

Patient and Methods: We describe the case of a woman who had been suffering from eyelid and peripalpebral dermatitis for four months. To treat her glaucoma, for a year she used several eyedrops for one year, switched by the ophthalmologist several times. She has also been reported oculorhinitis in March for some years. The patient underwent an allergological work-up consisting in prick test for inhalant allergens and patch tests with the G.I.R.D.C.A. series, benzalkonium chloride 0.1% aq., all the involved eyedrops and additional eyedrops ‘as is’.

Results: The patch test for the G.I.R.D.C.A. series and benzalkonium chloride as well as prick tests for the main inhalant allergens were negative. Only patch test performed for eyedrops containing timolol - alone or in association with other active ingredients - gave a positive response.

Conclusions: In our patient with eyelid and peripalpebral dermatitis, we have ruled out an allergy to the most common contact and inhalant allergens, while we have identified a cell-mediated hypersensitivity to timolol among the several eyedrops used by the patient.

Keywords: Allergic eyelid dermatitis; Contact dermatitis; Cell-mediated hypersensitivity; Patch test; Timolol

Introduction

Adverse reactions to ophthalmic products have been frequently observed. The most common are conjunctival manifestations and eyelid dermatitis. These reactions can be caused by both active ingredients and excipients [1,2]. The main responsible drugs are parasympathomimetics, sympathomimetics, beta-blockers, carbonic anhydrase inhibitors, prostaglandin inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs, and anesthetics [1,2].

Case Description

We describe the case of a 50-year-old teacher who had been suffering from eyelid and peripalpebral dermatitis for four months. To treat her glaucoma, she used several eyedrops for one year, including Ganfort® (bimatoprost+timolol), Azarga® (brinzolamide+timolol), Iopidine® (apraclonidine), and Qualid ofta® (brimonidine). After the appearance of dermatitis, the ophthalmologist switched eyedrops several times. For a short period she also stopped all eyedrops with an improvement of dermatitis. Subsequently, she introduced first Combigan® (brimonidine+timolol) and, then, Timolabak® (timolol) with a worsening of symptoms; therefore, these eyedrops were stopped.
Finally, Latanoprost® ratiopharm Italia (latanoprost) and Azopt® (brinzolamide) eye drops were introduced without an apparent worsening of symptoms.

She has also been reported ocular rhinitis in March for some years, but she denied other cutaneous diseases or allergic symptoms. The patient initially underwent an allergological work-up consisting in prick test for inhalant allergens and patch tests with the G.I.R.D.C.A. series. After a week, using Finn Chambers (SmartPractice, Phoenix, Arizona) fixed with Micropore® (3M Health Care, Borken, Germany), we patch tested benzalkonium chloride 0.1% aq., all the aforementioned eye drops ‘as is’, and additional eye drops [Saflutan® (tafluprost) and Lumigan® (bimatoprost)] ‘as is’. Patch tests were applied on the back and left for two days under occlusion, and readings were performed on day (D) 2 and 3 (Figure 1A). Positive patch test reactions (+, ++, or ++++) were determined according to the International Contact Dermatitis Research Group (ICDRG) criteria.

The patch test for the G.I.R.D.C.A. series and the prick tests for the main inhalant allergens were negative. Therefore, we have ruled out an allergy to the most common contact and inhalant allergens. The patch tests performed for Ganfort®, Azarga®, Combigan®, and Timolabak® eye drops were positive, while the patch tests carried out with Qualid ofta®, Azopt®, Lopidine®, Lumigan®, Latanoprost®, Saflutan® eye drops, and benzalkonium chloride were negative (Figure 1B) (Table 1). The patient subsequently began therapy with Saflutan® eye drop without experiencing any problems. Therefore, considering that the four patch tested positive eye drops contained timolol - alone or in association with other active ingredients - and that the other active ingredients of associations (bimatoprost, brimonidine, and brinzolamide) were negative when individually patch tested, we have concluded for a cell-mediated hypersensitivity to timolol.

**Table 1: Allergological investigation results.**

| PRICK TEST: | Readings at 15 minutes | D2 | D3 |
|-------------|------------------------|----|----|
| inhalant allergens | - | |

| PATCH TEST: | |
|-------------|---|
| G.I.R.D.C.A. series | |

| Eyedrops ‘as is’. |
|-------------------|
| Combigan® 2 mg/ml+5 mg/ml (brimonidine+timolol) | - | + |
| Ganfort® 0.3 mg/ml+5 mg/ml (bimatoprost+timolol) | + | ++ |
| Azarga® 10 mg/ml+5 mg/ml (brinzolamide+timolol) | +/- | ++ |
| Timolabak® 5 mg/ml (timolol) | - | + |
| Qualid ofta® 2 mg/ml (brimonidine) | - | - |
| Azopt® 10 mg/ml (brinzolamide) | - | - |
| Ipodine® 5 mg/ml (apraclonidine) | - | - |
| Lumigan® 2 mg/ml (bimatoprost) | - | - |
| Latanoprost® ratiopharm Italia 50 mcg/ml (latanoprost) | - | - |
| Saflutan® 2 mg/ml (tafluprost) | - | - |
| Benzalkonium chloride 0.1% | - | - |

**Discussion and Conclusions**

Allergic eyelid dermatitis is a common but often misdiagnosed disease that is related to eye drops, topical cosmetics or skin care products. Identification and elimination of causative agents is the mainstay of management. Allergic Contact Dermatitis (ACD) caused by eye drops is mainly attributable to active principles, but also excipients and the products “as is” should be tested. Our patient developed an ACD to timolol after almost a year. Timolol, a non-selective beta-blocker, is the most commonly used drug for the treatment of glaucoma and, for this reason, the most often involved in adverse reactions [3-5]. Patch test has proven to be a reliable method to identify an ACD caused by eye drops and it allows to reach a diagnosis faster, especially in cases of long-lasting symptoms and ongoing multiple therapies. If conjunctivitis and/or rhinitis are also present, we suggest to perform prick test for inhalant allergens.

**Figure 1 (A, B):** The patch tests performed for Qualid ofta®, Lopidine®, Ganfort®, Azarga®, Timolabak®, Combigan®, Saflutan®, Latanoprost® eye drops (from left, top to bottom) (A). The patch test reading performed after 3 days (72 hours) (B).
In conclusion, if we had overlooked the symptoms without performing an allergological evaluation, we would not have identified the responsible drug.

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**Conflicts of Interest**

All authors have no conflict of interest to declare.

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