

Cutaneous Allergy Testing in Patients Suspected of an Allergic Reaction to Eye Medication

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Key Words

Drugs • Allergy • Eye

Abstract

Purpose: Our aim was to determine the usefulness of allergy testing in patients with possible allergic reactions to an eye medication. **Methods:** This retrospective study analyzed the usefulness of allergy testing in 90 patients who on the basis of their complaints were under suspicion of having an allergic response to eye medication. **Results:** Among the 90 patients suspected of an allergic reaction to eye medication, the most common complaint was itching, while hyperemic conjunctivae were the most common symptom. Skin testing revealed an allergy to eye medication in 32 (36%) of the patients tested, which seemed to be the causal factor of the complaints in 22 cases (24%). The most frequent medication-associated allergies were directed against tobramycin, neomycin sulfate and thimerosal. Clinically relevant non-drug-related allergies occurred in 26 cases and were directed against nickel sulfate, *Myroxylon pereirae* and fragrance mix. Twenty-three patients were atopic and had positive skin prick tests against inhalation allergens such as house dust mites or dogs. **Conclusion:** Allergy testing was helpful to obtain a diagnosis of a clinically relevant allergy in 48 of the 90 patients who were referred under suspicion of having a contact allergy to eye medication.

Introduction

Ocular allergies can be induced by external antigens, e.g. seasonal rhinoconjunctivitis due to grass, or can be contact allergies due to topical drugs or cosmetics. Since the skin around the eye and the eyelids is very thin, contact allergens can easily penetrate. Therefore, the eyes and the eyelids in particular are especially sensitive to develop drug-induced contact dermatitis. Topical ophthalmic medications are known to play an important role in inducing contact dermatitis [1, 2], and patients with allergy-related problems are frequently seen in ophthalmic practices. However, reports on this phenomenon are infrequent.

Allergies can be classified on a clinical basis as immediate or delayed reactions, according to the time required for the reaction to occur after contact with the antigen [3]. Gell and Coombs classified hypersensitivity reactions into 4 physiologic categories [4]. Especially type I and IV hypersensitivity are relevant to the ocular surface. Type I depends on the interaction of antigen and humoral antibody (IgE) and tends to present as an 'immediate'-type reaction, like rhinoconjunctivitis or acute angioedema. Type IV reactions, on the other hand, are orchestrated by the cell-mediated immune arm of the immune response (T-cell-mediated) and have a delayed course of development. Drug-induced hypersensitivity of the eye is most

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often the result of a type IV allergic reaction (contact allergy). Type I drug-induced hypersensitivity also occurs, but less frequently, and is associated with acute chemosis and edema of the eyelids and conjunctiva [5].

The most prominent symptom of a drug-induced contact allergy is itching, while common signs are redness, conjunctival and eyelid edema, tearing, mucoid or mucopurulent discharge and papillary conjunctivitis. Dermatitis of the eyelids is typical of most contact allergies and can be due to the use of ophthalmic medications [1, 6]. In a study that focused on eyelid dermatitis, local inflammation was due to a nonspecific toxic irritation in 15–17% of the cases, while allergy was the cause of the dermatitis in 46–72% of the cases [6, 7]. The most frequent ocular allergies to medications were directed against thimerosal, neomycin sulfate and benzalkonium chloride [8]. Non-drug-related allergies known to cause ocular problems were directed to nickel sulfate, fragrance mix and phenylmercuric acetate.

The identification of the cause of an ocular allergy may lead to subsequent changes in medication or avoidance of the allergen. While other researchers only included patients with specific symptoms (e.g. periorbital dermatitis [8] or conjunctivitis and periorbital dermatitis [9]), we wanted to know how useful allergy testing was in all patients considered to have a possible ocular allergy against eye medication.

We set up a retrospective study to determine the usefulness of allergy testing in a set of patients under consideration for a possible allergy against eye medication, who had been tested dermatologically.

Patients and Methods

Between January 2000 and 2006, 90 patients were referred to the Department of Dermatology by ophthalmologists from the outpatient clinic of the Leiden University Medical Centre because of a suspected allergy to eye medication.

The patients were identified through the registration at the Department of Dermatology and studied retrospectively by searching Mirador, an electronic patient database used in the Leiden University Medical Centre. The following details were obtained from the patient's chart and Mirador: the patient's history, presenting signs and symptoms, medication used around the time that the patient was referred to the dermatologist, tests used and test results and final diagnosis. The data were collected and processed using Microsoft Excel.

Patch testing was performed with an extended European standard series and our self-composed ophthalmologic series of commercially available allergens (Van Der Bend, Brielle, The Netherlands) and drugs from our own pharmacy. Additional series like cosmetics series, cream and ointment series were also available.

Allergens were applied with Finn Chambers on Scanpor (Epitest Ltd. Oy, Tuusula, Finland) to the upper back, and the results were recorded after 2 and 3 days according to International Contact Dermatitis Group grading [10].

Skin prick tests were performed by the prick-through drop method on uninvolved skin at the flexor part of the right forearm with standardized aeroallergen extracts (Alk-Abello, Hørsholm, Denmark), with readings after 15 min.

All patients had agreed to the testing. All patients, but 1 (suspected of having an allergy to local anesthetics, which are not included in the test set), were tested for eye medication allergies using the ophthalmic series (89 patients tested). Depending on the patient's history, additional patch tests were added, like the European standard series (50 patients tested), cosmetic series, and cream and ointment series. When it was relevant to confirm or exclude an atopic predisposition, skin prick tests with standard inhalation antigens were performed (76 patients tested).

The research protocol followed the tenets of the current version of the Declaration of Helsinki (World Medical Association declaration of Helsinki 1964; ethical principles for medical research involving human subjects). As the analysis was retrospective, specific approval from the ethics committee at our institute was not necessary.

Results

A retrospective study was set up to determine the usefulness of allergy testing in patients with a possible allergic response to eye medication. Patients with possible allergy-related ocular complaints suffered from a variety of ocular conditions. The most common disease was glaucoma, which was present in 49 cases (54.4%), followed by cataract in 29 patients (32.2%), conjunctivitis in 24 (26.7%), and blepharitis in 17 (18.8%) (table 1). Several patients had multiple diseases.

Contact allergies of the eye can present with a range of possible signs and symptoms, of which the 3 main symptoms were itching (41 cases, 45.6% of all patients seen), a burning sensation of the eyes (18 patients, 20%) and pain around the eyes (13 cases, 14.4%; table 2).

Ten different potentially allergy-related signs were present in our patient group. The 4 most common symptoms were injected conjunctiva ($n = 45$), erythematous eyelids ($n = 40$), conjunctival or eyelid edema ($n = 34$) and eczema ($n = 34$). Other less frequent signs were: excessive tear production, erythematous maculae, blepharitis, conjunctivitis, dry eyes and dermatitis (table 3).

As mentioned above, the main objective of this study was to discover which percentage of the patients, who were sent in under suspicion of having a contact allergy to eye medication, had such an allergy (table 4). Of the 90 patients, 32 (35.6%) had an allergy to 1 or more kinds of

Table 1. Description of previous clinical ophthalmological diagnoses in 90 patients sent in for allergy testing

Diagnosis	Number of times seen
Glaucoma	49
Cataract	29
Conjunctivitis	24
Blepharitis	17
Pseudophakia	16
Ocular hypertension	13
Keratitis	11
Keratoconus	9
Uveitis	7
Dry eyes	7
Other diagnosis	36

Some patients had several previous diagnoses.

Table 2. Relation between the 4 most common symptoms and results of the tests

	Causal allergy to eye medication (n = 22)	Causal allergy not to eye medication (n = 26)	Irritant/toxic (n = 12)	No allergy (n = 30)
Itching (n = 41)	14	11	4	12
Burning (n = 18)	4	5	4	5
Pain (n = 13)	4	3	3	3
Blurry vision (n = 2)	0	0	1	1

One patient could have several symptoms at the same time (n = the number of times a problem occurred). Some patients presented with symptoms only.

Table 3. Relation between the 4 most common signs and results of the tests

	Causal allergy to eye medication (n = 22)	Causal allergy not to eye medication (n = 26)	Irritant/toxic (n = 12)	No allergy (n = 30)
Red conjunctiva (n = 45)	12	8	8	17
Red eyelid (n = 40)	13	9	5	13
Edema (n = 34)	8	9	4	13
Eczema (n = 34)	9	9	3	13
Excessive tear production (n = 17)	2	2	2	11

One patient could have several signs.

eye medication. In 22 (24.4%) of these cases, this contact allergy seemed to be the cause of the problems with which the patient presented, as the patient was currently using that medication. The majority of contact allergies were against antibiotics. In particular, allergies were directed against aminoglycosides. In the second place came preservatives. Only a few glaucoma drugs were being tested in the standard ophthalmic series (table 4). However, if an allergy against a glaucoma drug was suspected, that drug was tested specifically.

Besides nickel sulfate allergy (n = 11), patch tests revealed contact allergies for components of cosmetics like fragrances (n = 12) and *Myroxylon pereirae* (Peru balsam, n = 14). Twenty-five patients tested positive against inhalation allergens, of which the most common were: house dust mite in 12 cases (13.3%), dog in 11 (12.2%) and grass

in 10 (11.1%). In 26 cases (28.9%), these non-drug-related allergies were considered to contribute to or be the cause of their symptoms. The dermatologist determined that in 12 cases complaints were due to an irritant (toxic) contact dermatitis, caused e.g. by eye drops or contact lens solutions.

In 30 cases (33.3%), no contact allergy or toxic reaction against medication or other substances was found. The final diagnoses in these cases varied: 10 patients (11.1%) suffered from eyelid eczema without contact allergy, in 5 patients (5.6%) the problems were caused by chronic conjunctivitis e.c.i., while blepharitis was diagnosed in 2 (2.2%). Other diagnoses were rosacea in 4 cases (4.4%) and ectropion in 3 (3.3%). The remaining 6 patients (6.7%) were diagnosed as having dacryostenosis, cornea dystrophy, keratitis sicca, siliconomes and lentigo benigna.

Table 4. Testing for eye medications and percentage of tested individuals who developed a positive response

Type of eye medication	Patients tested	Positive patients	Positive %
<i>Glaucoma medication</i>			
Betagan (levobunolol)	4	1	25
Cosopt (timolol + dorzolamide)	17	3	18
Timolol	15	2	13
Xalatan (latanoprost)	17	1	6
<i>Antibiotics</i>			
Tobramycin	22	8	36
Gentamicin sulfate	23	6	26
Neomycin sulfate	90	7	8
Kanamycin sulfate	64	6	9
Framycetin	41	3	7
Polymyxin B sulfate	90	4	4
Kanamycin	22	1	5
Fusidic acid	65	2	3
<i>Other medications</i>			
Homatropine hydrobromide	3	2	67
Thimerosal	90	6	7
Benzalkonium chloride	90	4	4
Phenylephrine hydrochloride	65	2	3

Discussion

The main objective of this study was to discover which percentage of the patients who were sent in under suspicion of having a contact allergy to eye medication truly had such an allergy as the cause of their signs and symptoms. We observed 22 patients (24.4%) who indeed had a causal contact allergy to eye medication. Another 26 (28.9%) suffered from other allergies, which were considered the reason for their complaints.

Among the remaining 42 patients (46.7%), a range of other diagnoses was made, of which the most common were: irritant (toxic) drug reactions ($n = 12$), eczema e.c.i. ($n = 6$) and chronic conjunctivitis e.c.i. ($n = 5$). The high frequency of specific allergies is in contrast to the report from Wilson [1], who observed that 90% of the reactions to topical ophthalmic drugs should be considered to be an irritant contact dermatitis, as opposed to 10% which were due to a specific allergy. However, Wilson only looked at dermatitis, while we included all potential allergies against eye medication.

We observed a high percentage of positive responses with regard to antibiotics and glaucoma medication: 36 (9.1% of the times tested) positive reactions to antibiotics and 7 (13.7% of times the tested) to glaucoma medication.

Glaucoma medication had previously not been part of the standard test series but was evaluated when a specific allergy was suspected. On the basis of these results, many glaucoma drugs were recently added to our standard ophthalmic series. The most frequent positive reactions to glaucoma medication were against Cosopt ($n = 3$) and timolol ($n = 2$) and against frequently used preservatives in eye medication like thimerosal ($n = 6$) and benzalkonium chloride ($n = 4$; table 4). The most common allergies to antibiotics among our patients were against tobramycin ($n = 8$), neomycin ($n = 7$), gentamycin sulfate ($n = 6$) and kanamycin ($n = 6$), a drug not used for the eye, which is similar to previously published numbers [9]. Since Goossens [9] performed no allergy tests for glaucoma medication, there are no glaucoma medications in her list. We found remarkably few positive reactions to benzalkonium chloride in comparison to other studies; the reason for this is unclear.

Patients who responded positively to drugs often also responded to different allergens from the European standard series and additional series (64.5%).

In contrast, among the patients who did not have a drug-related allergy as the cause of their complaints, other allergies were often observed. Many of these patients were atopic or had multiple contact allergies, which made it difficult to recognize the causal allergen. It may therefore be that we underreport on the occurrence of specific allergies to eye medications.

The most common positive reactions to allergens from the skin prick test panel were against house dust mites, dogs and grass. The most frequent positive reactions from the European standard series were against *M. pereirae*, fragrance mix and nickel sulfate. These findings are similar to what other researchers reported [7–9, 11–15]. Therefore, it is rewarding to test with additional series like the European Standard series, cosmetic series, preservative series and the patients' own cosmetics.

When looking at the relationship between signs and symptoms compared to allergy, we observed that there was no sign or symptom that was specific to drug-associated allergy (tables 2, 3). While others only studied dermatitis, our study demonstrates that allergic responses of the conjunctiva and eyelids are also often related to specific eye medications. We advise testing for an eye-drug-related allergy whenever a patient is using eye medication and develops new signs and symptoms that fit the description of an allergy.

Conclusion

Twenty-two (24.4%) of the 90 patients tested had a causal contact allergy to eye medication. Through allergy testing, 26 cases (28.9%) of causal non-drug-related allergies were also diagnosed. Furthermore, the cause of the

irritation was a toxic reaction to different substances in 12 patients (13.3%). These results show that dermatological consultation in patients who were sent in under suspicion of having a contact allergy to eye medication was helpful in 60 of the 90 cases.

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