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Research Article

Allergic Contact Dermatitis from Ophthalmic Medications

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Abstract

Background: The skin of the eyelids is particularly susceptible to irritant dermatitis and allergic contact dermatitis, as the extremely thin skin in the eyelids may facilitate allergen penetration.

Objectives: To study contact allergy caused by topical ophthalmic medications in patients with periorbital dermatitis.

Methods: We retrieved allergic reactions to a patch test series consisting of ophthalmic medications and preservatives for the years 2002 - 2014 at the Helsinki University Central Hospital.

Results: 71 out of 622 tested patients (11.4%) had one or more allergic reactions in the ophthalmic patch test series. 23 of 622 tested patients (3.7%) had an allergic reaction to the antibiotic chloramphenicol. Of 448 patients, 14 (6.1%) had an allergic reaction to the preservative thimerosal. Other common allergens in the test series were anti-glaucoma agents timolol (2.6%), latanoprost (1.6%) and dorzolamide (1.1%), mydriatic agent phenylephrine (1.8%), and the preservative benzalkonium chloride (1.6%).

Conclusions: Patch testing is encouraged in all patients in which periorbital contact dermatitis is suspected in order to identify allergens causing contact dermatitis of the eyelids. Especially in those who are using any kind of ophthalmic medication as e.g. glaucoma drugs.

Keywords: *Allergic Contact Dermatitis; Delayed Type-Sensitivity; Ophthalmic Medications; Preservatives; Periorbital Dermatitis; Patch Testing*

Introduction

Contact allergy is a common cause of periocular dermatitis [1]. The skin of the eyelids is particularly susceptible to allergic and irritant contact reactions, as the extremely thin skin in the eyelids may facilitate allergen penetration [2].

The most relevant allergen sources are the patients personal products, such as facial cream, eye shadow and ophthalmic therapeutics [1]. Here we present an analysis of patients with patch test positive reactions to ophthalmic medications in a central university dermatology clinic and describe the most common allergens caused by ophthalmic medications.

Materials and Methods

This was a retrospective study based on clinical investigations of patients suspected of having periorbital contact dermatitis caused by ophthalmic medications or cleansing solutions. The patients referred to the Helsinki University Central Hospital were patch tested with Finn Chambers® (SmartPractice, Phoenix, USA), and readings were performed two or three times, depending on the day of application (D2, D3 and D4; D2, D3 and D6; or D2 and D5) according to the recommendations of the International Contact Dermatitis Research Group [3].

We screened the test files from January 2002 to the end of 2014 for allergic reactions to the ophthalmic medications patch test series. The providers of the test materials varied, and the composition of the ophthalmic patch test series has varied over the years. The concentrations and the numbers of tested patients and allergic reactions for each test substance in the patch test series are shown in table 1. The clinical records of all patients with at least one allergic reaction (+/++/+++) to any of the compounds in 2002 - 2014 were analysed for the patients age, gender, dermatologic and ophthalmologic diagnoses, other contact allergies, skin prick test results and the results of cytologic samples from the upper and lower lid conjunctiva [4]. The clinical relevance of the of the positive patch test results was evaluated.

Allergen	Provider	Concentration	Number of patients tested	Allergic reactions, no. (%)
Antibiotics				
Chloramphenicol	Chemotechnique	5% pet.	622	23 (3.7)
Fusidic acid	Chemotechnique	2% pet.	619	1 (0.2)
Levofloxacin	Santen	5 mg/ml	346	1 (0.3)
Polymyxin b sulphate	Trolab	3% pet.	619	4 (0.6)
Local anesthetics				
Oxybuprocaine Hydrochloride	Chauvin Pharmaceuticals	4 mg/ml	366	2 (0.5)
Tetracaine	Chemotechnique	5% pet.	615	4 (0.7)
Anti-glaucoma medication				
Brimonidine tartrate	Allergan Pharmaceuticals	2 mg/ml	366	2 (0.5)
Pilocarpine nitrate	Chauvin Pharmaceuticals	20 mg/ml	345	0 (0)
Timolol	Santen	5 mg/ml	349	9 (2.6)
Dorzolamide	Teva	20 mg/ml	369	4 (1.1)
Latanoprost	Ratiopharm	50 µg/ml	366	6 (1.6)
Other				
Atropine sulphate	Chauvin Pharmaceuticals	1 %	613	3 (0.5)
Phenylephrine hydrochloride	Chauvin Pharamaceuticals	100 mg/ml	607	11 (1.8)
Scopolamine	Santen	2,25 mg/ml	605	3 (0.5)
Tropicamide	Santen	5 mg/ml	582	3 (0.5)
Benzalkonium chloride	Trolab	0.1% pet.	617	10 (1.6)

Table 1: *Most frequent allergens in patients with periorbital dermatitis.*

Results

During the study period, the ophthalmic medications patch test series was tested on 622 patients which were referred after ophthalmologic examination. Of these, 71 (11.4%) had an allergic reaction, the details of whom are shown in table 2. 59 (83%) were females and 12 (17%) males. The mean age was 57 years at the time of testing. Skinprick-tests were performed on 55 patients and out of these, 25 patients (45%) had at least one positive reaction. 23 had a history of atopic eczema, 26 did not have a history of atopic eczema, and 22 were undetermined. The positive patch test reactions were evaluated to be clinically relevant in 38 patients, and not relevant in 30 patients. From the patient files, positive patch test reactions to topical ophthalmic drugs could be verified in most cases, but none of the positive reactions to thimerosal were considered clinically relevant in our data. Cytologic samples from the upper and lower lid conjunctiva were taken from 23 patients. In 15 samples the cytology was consistent with dry eye, and in 10 samples there was conjunctival eosinophilia suggesting an allergic reaction. 20 patients suffering from dry eye were diagnosed by an ophthalmologist. 32 had glaucoma, and this

group had about half of all positive reactions. Of the 71 patients, 43 patients had positive reactions in also other patch test series, and 15 had not. The most common other allergens were nickel sulphate (17 patients), fragrance mix (15 patients), and the antibiotic neomycin (12 patients).

	Yes	%	Not available
Females	59	83	0
Age over 40 years	61	86	0
Atopic eczema	23	32	22
IgE-mediated allergies	25	35	16
Glaucoma	32	45	2

Table 2: *General information of patch test positive population (n = 71).*

The most common allergen in the ophthalmic medication patch test series was chloramphenicol, 3.7% (23 patients). Other common allergens were anti-glaucoma agents timolol, (9 patients, 2.6%), latanoprost (6 patients, 1.6%) and dorzolamide (4 patients, 1.1%), the mydriatic agent phenylephrine (11 patients, 1.8%), and the preservative benzalkonium chloride (10 patients, 1.6%). All together 21 patients out of 71 had a positive reaction to glaucoma medications. The preservative thimerosal has not been included in the ophthalmic medication patch test series after 2005 since it is no longer used in ophthalmic medications in Finland. Of the 448 patients tested between 2002 and 2005, 14 (6.1%) had an allergic reaction to the thimerosal. None of these 14 patients had used eye drops containing thimerosal, and none of the reactions were considered related to the patients periorbital dermatitis. Furthermore, cromoglycate eyedrops were tested on 21 patients, and the antihistamines emedastine, azelastine, olopatadine were tested on 9 patients each and ketotifen on 11 patients. No allergic reactions were identified for any of these five allergy medications.

Discussion

This study focused on characterising the subgroup of patients referred for periorbital dermatitis with a positive patch test to ophthalmic medications during a span of 13 years. The characteristics of our patient population is similar to that of patients with periorbital dermatitis overall. A predominance of females among patients with periorbital dermatitis is well known from the literature [2,5-10]. The portion of females in our study (83%), is similar to that reported from studies in Germany, Switzerland and Austria (81%) [5], southern Europe (90%) [6], and the United States (87%) [2]. The female predominance has been attributed to the more common use of cosmetics and other topical products on the face.

The mean age of patch tested patients with periorbital dermatitis has varied in previous studies from 44 years to 73 years [5,11]. In our study, the mean age of the patch test positive population was 57 years. Approximately half of the patient population had glaucoma, and 20 patients had dry eyes, which may be related partly to the age and partly to the ophthalmic drug itself. The mean age of the subpopulation with glaucoma was 65 years. Positive skin prick tests are not directly connected to allergic contact dermatitis, but may represent atopic skin diathesis, and thus susceptibility to irritant skin reactions. Atopic eczema of the eyelids may occur as a confounding factor or even in combination with contact dermatitis.

Periorbital dermatitis connected to the use of topical ophthalmologic drugs may be either allergic or irritant dermatitis. In this study, contact allergy to these medications was seen in 11% of cases. This indicates that the suspected allergic dermatitis is, in fact, irritant in many cases. Irritants skin reactions cannot be tested by allergy tests, i.e. patch testing.

The finding that a large portion of the patients suffered from dry eyes has not described in the previous similar studies [5,7,11]. It was both one of the most common clinical diagnoses and was seen in the majority of the cytological samples. Dry eye is a common finding in glaucoma patients and in ocular allergies. In glaucoma patients dry eye syndrome can be related to a higher age of the patients, to many

glaucoma drugs as well as to chronic allergic inflammation. Almost half of the patch test positive patients were diagnosed with glaucoma, which is probably linked with the finding that anti-glaucoma medication was a leading group of allergens in the patch test results. Long-term use of anti-glaucoma medication has also been positively correlated with dry eye syndrome [12]. Signs of eosinophilia or dry eye syndrome in the cytologic samples may suggest changing the ophthalmic medication.

Allergic eyelid contact dermatitis is almost always connected with concomitant allergic conjunctivitis which is seen in many cases as red eyes and often with conjunctival eosinophilia. Conjunctiva penetrates well many eyedrops including antiglaucoma medication. This may partly explain the negative skin tests which in some cases are not sensitive enough to prove the contact allergy. Many are also irritant reactions were the allergy tests are negative. However after stopping the suspected medication there is complete recovery of the symptoms.

Recently, Landeck., *et al*. published a study of an ophthalmic patch test series on patients with periorbital dermatitis in Germany, Switzerland and Austria [5]. However, the composition of the patch test series was somewhat different from the one used in this study. In the results from Landeck., et al. the antibiotics (gentamycin, neomycin, and kanamycin) were the leading group of allergens. As the antibiotics mentioned above are not frequently used in ophthalmic medications in Finland, they were not included the ophthalmic medication patch test series. Neomycin and gentamycin are however used in other than ophthalmic medications in Finland.

The leading allergen in our population was the antibiotic chloramphenicol, which is the most commonly used ophthalmic antibiotic in Finland [13], while the antibiotics fusidic acid and levofloxacin only had 1 positive reaction each even though both are frequently used in Finland, and polymyxin B sulphate had 4 positive reactions. An increased frequency of sensitization to antibiotics among patients with periorbital dermatitis has been described previously in the literature and can be attributed to their widespread use in and around the eyes [5-8,14].

Anti-glaucoma medications were the second most common allergen group after the antibiotics. Timolol, dorzolamide and latanoprost accounted for 19 of the 21 positive reactions, while no allergic reactions were recorded for pilocarpine and 2 for brimonidine. Some authors have outlined the difficulties with obtaining positive results with beta blockers and dorzolamide [15-17]. This suggests that glaucoma drugs may also act as irritants [18].

Benzalkonium chloride is the only preservative in the ophthalmic patch test series used to date. It is used in several ophthalmic medications including an antihistamine sold over the counter, as well as in some contact lens liquids. Benzalkonium chloride is also a well-known irritant [19]. Thimerosal was included in the patch test series until 2005. However, the clinical relevance of thimerosal in periorbital dermatitis has been stated as low [4,5,20]. As many patients in our data probably have been vaccinated with vaccines containing thimerosal, the sensitization to this allergen does not necessarily reflect ophthalmological problems.

Conclusion

Antibiotics and anti-glaucoma medications constitute the main source of sensitization in patients with contact allergy to ophthalmic medications, however, large differences between different antibiotics as well as different anti-glaucoma medications could be found. Common ophthalmic problems seen in patients with contact allergy are dry eyes and glaucoma. Patch testing is encouraged in all patients in which periorbital contact dermatitis is suspected in order to identify allergens causing contact dermatitis of the eyelids. Especially in those who are using any kind of ophthalmic medication as e.g. glaucoma drugs.

Author Contributions

All the authors have contributed in the study, interpretation of the data and preparation of the manuscript and have approved it.

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