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REVIEW ARTICLE

Allergic contact dermatitis from ophthalmicsYue Zheng¹, Paru R. Chaudhari², and Howard I. Maibach³

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Abstract

In this article we summarize the recently described allergens responsible for allergic contact dermatitis due to ophthalmic drugs and contact lens solutions, and emphasize the need on how to perform diagnostic testing in this special clinical entity.

Keywords

Allergic contact dermatitis, ophthalmics, ophthalmologics

History

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We previously reviewed causes of allergic contact dermatitis from use of ophthalmic drugs and contact lens solutions^{1–3}. Here, we update this information. Epidemiologic data among periorbital dermatitis patients demonstrates significant predominance of women (87.6%) and of individuals aged 40–59 years (45.9%). Nickel (16.5%) and fragrance mix (13.2%) were top-ranking sensitizers⁴ but are often of unknown clinical relevance. Older subjects with periorbital dermatitis tend to be triggered by topical medications, while young women have increased rates of skin atopy and allergies, particularly from cosmetic and skin care products. The prevalence of sensitization to ophthalmic allergens is generally less than that to environmental allergens⁵ presumably because of decreased exposure.

Recently described allergens responsible for allergic contact dermatitis due to ophthalmic drugs and contact lens solutions are summarized in the Table 1.

Although most reports fall under drug classifications previously described, carbonic anhydrase inhibitors, beta-blockers, α_2 -adrenergic agonists, nonsteroidal anti-inflammatory drugs, epinephrine and possibly benzalkonium remain relevant allergens. Eye drops containing retinoic acid, epsilon-aminocaproic acid, vitamin K1, latanoprost, dorzolamide, timolol and phenylephrine-inducing contact dermatitis have recently been reported.

Contact dermatitis due to the carbonic anhydrase inhibitor, dorzolamide, has reported at least six times. Only two cases of contact dermatitis has been reported as a result of prostaglandins. Clinical patch test data from 2001 to 2010 were analyzed by Landeck et al in 4779 periorbital dermatitis patients; highest rates of allergic contact dermatitis were found due to topical ophthalmic medications (34.7%)⁵. Ingredients in topical ophthalmic medications including preservatives, antiglaucoma medications (prostaglandin analogs, β -blockers, carbonic anhydrase inhibitors, parasympathomimetics, sympathomimetics), anti-inflammatory medications (nonsteroidal anti-inflammatory drugs, corticosteroids), antibiotics, antivirals, anti-allergic medications (antihistamines, cromones), anesthetics, mydriatics and cycloplegics caused periorbital contact dermatitis and allergic conjunctivitis⁶. Among the main preservatives used in ophthalmic preparations, benzalkonium chloride (BAC), thimerosal, parabens and chlorhexidine are common causes of allergic reactions⁷. Phenylephrine, an effective ingredient in mydriatic eyedrops, has been reported to cause allergic contact conjunctivitis, eyelids' edematous swelling and periorbital dermatitis^{8–9}. Numerous reports document eyedrops containing phenylephrine hydrochloride causing allergic contact dermatitis, systemic contact dermatitis and long-lasting allergic contact blepharoconjunctivitis^{10–13}. The mucolytic, *N*-acetylcysteine, used to alleviate dry eyes, has recently been reported to cause allergic contact dermatitis. Allergic contact dermatitis caused by topical eyedrops containing latanoprost also been found repeatedly^{14–16}.

Routine and alternative patch testing were also performed on these patients. Erdmann patch tested with the European

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Table 1. Allergic compounds (update 2016).

Allergen [group]	PT concentration (%)	vehicle	PT-positive cases	PT-negative cases	References
<i>Carbonic anhydrase inhibitors</i>					
Dorzolamide	5%, 10%	aq	1 cd	0/5	Shimada et al. ²⁵
	10%, 15%	pet	1 cd	0/5	Shimada et al. ²⁵
	Eyedrops 2%	as is	1 cd	0/16	Mancuso and Berdondini ²⁶
	0.0001%, 0.001%, 0.01%, 0.1%, 2%	aq	1 cd	0/16	Mancuso and Berdondini ²⁶
	40%	aq	1 cd	0/10	Kalavala and Statham ²⁷
	Eyedrops 2%	as is	2 cd	0/20	Aalto-Korte ²⁸
	0.05%, 1%	pet	1 cd	ND	Aalto-Korte ²⁸
	5%	aq/pet	2 cd	0/10	Mata et al. ²⁹
	Eyedrops 1%	as is	1 cd	ND	Lee et al. ³⁰
<i>Antioxidants</i>					
Pirenoxone	Eyedrops (Catalin K)	as is	1 cd	ND	Inui et al. ³¹
	0.005%, 1%	aq	1 cd	ND	Inui et al. ³¹
Sodium bisulfite	Eyedrops (Tathion)	as is	1 cd	0/10	Nagayama et al. ³²
	1%, 0.2%	aq	1 cd	ND	
<i>Prostaglandins</i>					
Latanoprost [PG]	Eyedrops (Xalatan)	as is	1 cd	ND	Jerstad and Warshaw ²⁰
	0.005% Eyedrops (Xalatan®)	as is	1 cd	ND	Lee et al. ¹⁶
<i>Antibiotics</i>					
Vancomycin	0.005%, 5%	aq	1 cd	ND	Hwu et al. ³³
Azithromycin	Azydrop®, 1%, 5% 10%	as is, pet	1cd 1cd	ND 0/10	Flavia Monteagudo et al. ³⁴
<i>Beta-blockers</i>					
Carteolol	1%, 2%	aq	1 cd	0/23	Sanchez-Perez et al. ³⁵
	Eyedrops	as is	1 cd	0/5	Quirarte et al. ³⁶ , Jappe et al. ³⁷ , Gonzalo-Garjito et al. ³⁸
<i>Corticosteroids</i>					
Nonsteroidal Anti-inflammatory drugs	CS-containing preparations	ocular	18 cd	297/315	Baeck et al. ³⁹
Trometamol	1%, 0.50%, 0.10%, 0.05%	aq	1 cc/cd	ND	Bohn et al. ⁴⁰
Diclofenac sodium	5%, 1%, 0.5%, 0.1%, 0.01%	pet	1 cd	ND	Miyazato et al. ⁴¹
<i>Antihistamines</i>					
Pheniramine maleate	1%	aq	1 cc/cd	ND	Parente et al. ⁴²
<i>A2-adrenergic agonists</i>					
Apraclonidine	Eyedrops	as is	1 cc	0/20	Silvestre et al. ⁴³
	10%	aq	1 cc	0/20	Silvestre et al. ⁴³
	Eyedrops 1%	as is	31/64 cc/cd	ND	Butler et al. ⁴⁴
Brimonidine	Eyedrops 0.2%	as is	1 cc	ND	Sodhi et al. ⁴⁵
Timolol	0.5% Eyedrops (Timofol) 5%, 10%	as is pet, pet	1 cd	0/5	Otero-Rivas ⁴⁶
<i>Mucolytics</i>					
N-Acetylcysteine	10%	aq	1 cd	0/14	Davison and Wakelin ⁴⁷
<i>Anaesthetics</i>					
Proparacaine	0.5%	pet	1 cd	ND	Dannaker et al. ⁴⁸
<i>Epinephrine</i>					
Neosynephrin POS	Dorzolamide eyedrops 5%	as is	1cd	ND	Erdmann et al. ¹⁰
Phenylephrine hydrochloride	1.0%	aq	1 cd	ND	Erdmann et al. ¹⁰
	Eyedrops(Mydrin®-P)	as is	1 cd	ND	Tamagawa-Mineoka et al. ¹¹
	5.0%	pet	1 cd	ND	Tamagawa-Mineoka et al. ¹¹
	10%.(Trolab)	aq	134 cd	630/764	Madsen et al. ¹³
<i>Others</i>					
Bismuth oxide	5%, 2%, 0.5%	pet	1 cd	0/10	Wictorin and Hansoon ⁴⁹
	Ointment (Noviform)	as is	1 cd	0/10	Wictorin and Hansoon ⁴⁹
Parabens	Eyedrops (Clarvisan)	as is	1 cc/cd	0/25	Vilaplana and Romaguera ⁵⁰
	3%	pet	1 cc/cd	0/25	Vilaplana and Romaguera ⁵⁰
Benzalkonium chloride	0.1%	pet	87 cd	4335/4422	Uter et al. ⁵¹
	0.15%	aq, pet	2 cd,0 cd	8/10,10/10	Benjamin et al. ¹⁹
Benzethonium chloride	0.05%, 0.15%	aq, pet, aq, aq	0cd,1cd	10/10,9/10	Benjamin et al. ¹⁹
	0.15%, 0.5%	as is	1cd, 2cd	9/10,8/10	
Retinoic acid	Cream ((ReTrieve)	as is	1cd	ND	Anderson et al. ²⁰
Epsilon-aminocaproic acid	Excipient in eyedrops (Hyalein Mini)		1cd	ND	Sukegawa et al. ⁵²
Vitamin K1	Eye cream, 2%	as is,urea	1cd1cd	0/20	Lopez-Lerma et al. ⁵³

cc: contact conjunctivitis; cd: contact dermatitis; pet: petroleum; aq: aqueous; ND: not done; PT: Patch test.

standard and found that phenylephrine hydrochloride showed positive reactions⁸. Landeck et al used their ophthalmic tray consisting of seven preservatives, six antibiotics and three other ophthalmic agents on 1158 periorbital dermatitis

patients and found antibiotics (gentamicin, neomycin, kanamycin) the leading allergens, while patch testing with preservatives often elicited irritant or weak positive reactions. They suggested that preservatives cannot be regarded as

common allergens, while antibiotics more often cause true allergic reactions necessitating avoidance¹⁷. Gonzalo-Garijo reported a case of positive patch reaction of phenylephrine and pseudoephedrine in a erythroderma patient induced by pseudoephedrine¹⁸. Anderson et al documented bilateral periorbital dermatitis caused by retinoic acid that was confirmed by patch testing¹⁹. BAC (0.15% aq), BAC (0.15% pet), BEC (0.05% aq), BEC (0.15% pet), BEC (0.15% aq), BEC (0.5% aq) was tested via patch testing and two of eight patients showed positive reaction. Possible cross-reaction occurred between BAC and BEC²⁰. As BAC is an irritant, confirmation use testing (ROAT) is advisable²¹.

Testing ingredients of ophthalmics is particularly important in the diagnosis of allergic reactions. An international standardization of ophthalmic trays is useful in defining potential allergen and avoid recurrences. Until such a series is commercially available, many ophthalmic intolerant patients will not be tested, resulting in often prolonged discomfort (and exposure) of the trial and error elimination and satisfaction methodology, as well as the potential loss of public health information. Commercially available patch test allergens and pharmaceutical manufacturers providing new ophthalmics would aid diagnosis. Optimal concentrations and vehicles remain to be defined¹⁸.

Corazza et al concluded that negative patch testing is extremely common, even with a suggestive positive history of an allergic reaction due to ophthalmics²². Patch testing is a criterion standard for diagnosing allergic contact dermatitis. Other diagnostic tests included repeat open application tests (ROATs), lymphocyte transformation tests (LTTs), skin prick tests. Stripping and scratching the area of skin could aid accurate diagnosis²¹.

ROATs can be used to verify that an antigen causing a positive patch test will lead to dermatitis when dosed at usage concentrations. Xalatan (latanoprost) 0.005% ophthalmic solution-induced allergic contact dermatitis was confirmed via ROATs²⁰.

LTT is an *in vitro* test to detect the cause of allergic contact sensitization. APTs that are performed by applying protein allergens in an occlusive chamber for 48 h are more frequently used in AD patients. Skin prick tests, stripping and scratching the area of skin could increase absorption and enhance accuracy. Erdmann tested neosynephrin POS 5% eyedrops as is on stripped skin and found positive reaction¹⁴. Akita et al. observed positive reaction of phenylephrine hydrochloride in eyedrops utilizing closed scratch-patch test and long-lasting allergic patch test whether negative reaction in routine two-day closed patch test²³. Pretreatment with sodium lauryl sulfate (SLS), an anionic surface-active agent, has been found effective method of patch testing. SLS may increase antigen presentation of the allergen and sensitivity to patch testing²⁴. With all of the above, appropriate irritant controls and clinical interpretation are mandatory.

In conclusion, if an allergic reaction is suspected, even after a negative patch test, repeating the test using the scratch method, an increased drug concentration, or application of SLS are all viable options. Multicenter trials of these methods should aid their refinement, leading to increased accuracy. ROAT to one eye remains cumbersome, but a highly clinically relevant assay.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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