

Hypersensitivity Reactions to Ophthalmic Products

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Abstract: Adverse reactions after administration of ophthalmic products have frequently been observed. These reactions can be provoked by both active principles and excipients. Different pathogenic mechanisms have been suggested for such reactions, including immunologic ones. Basophils and mast cells participate in IgE-mediated reactions through the release of mediators like histamine and tryptase, whereas a T-cell-mediated pathogenic mechanism is involved in most delayed reactions, particularly conjunctival ones and eyelid dermatitis. Prick tests and immediate-reading intradermal tests are carried out to diagnose immediate hypersensitivity reactions, while patch tests are usually performed to evaluate delayed reactions. Other diagnostic tests, such as serum-specific IgE assays in immediate reactions, as well as delayed-reading intradermal tests and/or lymphocyte transformation tests in delayed ones, are rarely performed.

In this review, particular attention is addressed to the clinical and practical aspects of both cell-mediated and IgE-mediated hypersensitivity reactions to ophthalmic products.

Key Words: ophthalmic products, eye drops, preservatives, hypersensitivity reactions, patch tests.

INTRODUCTION

Adverse reactions to ophthalmic products have frequently been observed [1]. The most common are conjunctival manifestations and eyelid dermatitis. These reactions can be provoked by both active principles and excipients. Parasympathomimetics, sympathomimetics, β -blockers, carbonic anhydrase inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anesthetics are the main responsible drugs (Table 1).

With regard to eyelid dermatitis, a recent review [2] displayed a similar percentage of irritant and allergic types. In particular, 5 studies demonstrated that 11-39.5% of patients with eyelid dermatitis had an atopic eczema, but it was commonly associated with other conditions, especially seborrheic dermatitis, metal or protein contact dermatitis, and *Staphylococcus aureus* infection [3]. Generally, patients with these reactions had chronic ocular diseases (e.g., allergic conjunctivitis, ocular inflammation), which need repeated administrations of eye drops for diagnostic and therapeutic ends; for this reason, they are particularly exposed to the risk of sensitization to these compounds [4]. Another local risk factor is the use of contact lenses. Systemic risk factors are female gender, a history of allergic diseases, and use of systemic drugs such as antihypertensives, hypoglycemics, steroids, and NSAIDs [5].

Our study is aimed at highlighting the risk of hypersensitivity reactions to ophthalmic products on the basis of the numerous cases reported in the literature, as well as at indicating the proper management of such reactions.

Pathogenic Mechanisms

The revised nomenclature for allergies [6], which is based on the mechanisms that initiate and mediate hypersensitivity reactions, classifies such reactions to drugs as either allergic or non-allergic. The former are mediated by immunologic mechanisms, either antibodies or cells; all other reactions should be referred to as non-allergic drug hypersensitivity. In addition, allergic reactions to drugs are classified as IgE-mediated or non-IgE-mediated. In IgE-mediated reactions, the drug or drug metabolite reacts with IgE bound to the surface of mast cells and leads to activation, degranulation, and release of mast cell vasoactive mediators like histamine and tryptase. Some non-IgE-mediated reactions are cell-mediated. In the latter reactions, CD4⁺ and CD8⁺ T cells recognize drugs through their $\alpha\beta$ receptors [7]. Drug-specific T cells orchestrate inflammatory skin reactions through the release of various cytokines (e.g., interleukin-5, interferon) and chemokines (e.g., interleukin-8). Activation of T cells with a particular function seems to lead to a specific clinical picture; for example, a large number of cytotoxic CD8⁺ T cells in the epidermis is associated with the formation of vesicles and bullae.

Non-allergic hypersensitivity reactions to drugs may involve different pathogenic mechanisms. Reactions associated with NSAIDs have been attributed to their inhibitory effect on cyclooxygenase (COX)-1. Atropine can provoke non-allergic hypersensitivity reactions because of its capability of releasing histamine through a non-immunologic mechanism.

Allergologic Work-Up

Prick tests and immediate-reading intradermal tests are carried out to diagnose immediate hypersensitivity reactions to ophthalmic products, while patch tests are usually performed to evaluate delayed reactions like eyelid dermatitis.

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Other diagnostic tests, such as serum-specific IgE assays in immediate reactions, as well as delayed-reading intradermal tests and/or lymphocyte transformation tests (LTT) in delayed ones, are rarely performed. In case of negativity of these tests or suspected non-allergic hypersensitivity, provocation tests with responsible drugs can be carried out.

Table 1. List of Ophthalmic Products Most Involved in Hypersensitivity Reactions

Parasympathomimetics (atropine, homatropine, cyclopentolate, pilocarpine)
Sympathomimetics (phenylephrine, dipivefrine, pseudoephedrine, apraclonidine)
β-blockers (betaxolol, carteolol, metipranolol, timolol, befunolol)
Carbonic anhydrase inhibitors (dorzolamide)
Prostaglandin analogs (latanoprost)
Antibiotics Aminoglycosides (tobramycin, gentamicin, sisomicin) Polypeptides (rifamycin) Sulfonamides (sulfacetamide) Vancomycin
Antivirals (acyclovir, interferon- β , idoxuridine, trifluoridine)
NSAIDs (indomethacin, diclofenac, ketorolac)
Anesthetics (proparacaine, tetracaine)
Antiallergic drugs (pheniramine maleate, sodium cromoglycate, N-acetyl-aspartyl glutamic acid, amlexanox)
Other ϵ -aminocaproic acid Penicillamine N-acetylcysteine Bismuth Papain Rubidium iodide Hyaluronidase
Preservatives (thimerosal)

Often culprit allergens are not identified for several reasons [8]: 1) many ophthalmologists switch the medication without investigating a possible sensitization to the suspected compound; 2) up-to-date standardized ophthalmic patch tests are lacking; 3) some suspected compounds are not available in a pure form; 4) conventional patch test techniques may not detect ophthalmic contact allergies; and 5) irritability of the periorbital region may mimic contact allergy.

PARASYMPATHOMIMETICS

Parasympathomimetic drugs are natural and synthetic alkaloids that inhibit acetylcholine by competition on the receptor sites. They include atropine, scopolamine, homatropine, tropicamide, and cyclopentolate.

Systemic adverse effects of these agents include nausea, vomiting, sweating, tachycardia, and bronchospasm, whereas

adverse ocular events include blurred vision, lens opacities, eyelid eczema, conjunctivitis, and, rarely, retinal detachments.

Atropine is the most widely used parasympathomimetic agent, particularly in children. Its topical use is mainly restricted to ophthalmological preparations, chiefly as mydriatic eye drops. Patients with adverse reactions to atropine frequently report serious systemic reactions. This suggests an IgE-mediated pathogenic mechanism or atropine's capability of releasing histamine through a non-immunologic mechanism. Cases of anaphylaxis induced by atropine have been described [9]. A strongly positive response to atropine intradermal testing was observed in a 38-year-old woman who had an anaphylactic shock after intravenous atropine.

Cell-mediated hypersensitivity reactions to parasympathomimetics have also been reported [10, 11]. In particular, in their review of patients with a contact allergy to mydriatic agents, Decraene *et al.* [11] described 10 cases (6 reacted to phenylephrine, 5 to atropine, and 3 to homatropine) diagnosed on the basis of patch-test positivity. Simultaneous positive responses to atropine and homatropine occurred in 2 subjects, and to phenylephrine and either atropine or homatropine in 2 others. Unfortunately, not all patients were tested with all 3 compounds. Contact allergy to atropine frequently had occurred after surgery (4 out of 5 patients), where it is used because of its long-acting effect. The reactions to chemically-related mydriatic agents are probably due to cross-reactivity. However, patients using multiple ophthalmic products may also become concomitantly sensitized. Allergic reactions to topically applied cyclopentolate are very rare. In the case reported by Muñoz-Bellido *et al.* [12], clinical features and positive results at 15- and 30-minute readings of patch testing with cyclopentolate hydrochloride allowed the diagnosis of contact urticaria. Only 3 cases of allergic contact dermatitis to pilocarpine confirmed by patch tests have been reported [13-15]. In particular, one subject reacted positively after repeated open application tests [15].

SYMPATHOMIMETICS

The sympathomimetic drugs derive from only one precursor, β -phenylethylamine, consisting of a benzene ring with an ethylaminic side chain. The most used are adrenaline, or epinephrine, phenylephrine, and apraclonidine.

Villarreal [16] evaluated 37 patients with adverse reactions to phenylephrine; 29 of them were finally diagnosed as allergic to this drug: 22 by patch testing and the remaining 7 by conjunctival challenges, which were performed in patients displaying patch-test negativity. In performing such challenges, the drug was introduced into the conjunctival sac at increasing concentrations up to undiluted eye drops. Readings were both immediate (after 1 hour) and late (after 1 and 2 days) at each concentration.

Thomas *et al.* [17] studied a patient with 2 episodes of blepharoconjunctivitis and periocular dermatitis due to phenylephrine in eye drops, observing positive responses to the culprit drug in both patch tests and LTTs.

Recently, Gonzalo-Garijo *et al.* [18] described a patient with contact dermatitis due to phenylephrine and an erythrodermia due to pseudoephedrine. A cell-mediated hypersensi-

tivity to both drugs was diagnosed on the basis of positive responses to patch tests.

Erdmann *et al.* [19] studied a 62-year-old man with symmetrical eyelid dermatitis, related to the use of eye drops with phenylephrine hydrochloride for glaucoma. A delayed-type hypersensitivity to phenylephrine was diagnosed by patch testing. They did not find cross-reactivity with closely related and structurally similar drugs, such as epinephrine and ephedrine.

Allergic contact dermatitis caused by dipivefrine, a pro-drug of epinephrine, has rarely been reported. Parra *et al.* [20] described a 68-year-old man with glaucoma, treated for 3 years with timolol and dipivefrine in his right eye and only timolol in the left one, who had suffered eczema around the right eye in the past year. Patch tests were positive to both dipivefrine and epinephrine after 4 days. We must consider that, in the eye, dipivefrine is de-esterified to epinephrine.

Vilaplana *et al.* [21] described a patient with allergic contact dermatitis due to dipivefrine, who was patch-test positive to the culprit drug and weakly positive to epinephrine at the 2-day reading; he became negative to the latter drug at the 4-day reading.

Akita *et al.* [22] described a patient with symptoms of conjunctivitis and an eruption around his eyes a few hours after administration of eye drops containing phenylephrine 5%. They used 3 types of closed patch tests in their allergologic work-up: 1) 2-day patch tests (routine method), 2) 2-day stripped patch tests (stripping performed 10 times using Micropore), and 3) 2-day scratch-patch tests. Only the scratch-patch test produced a positive result.

Adverse reactions to topical solutions of 1.0% apraclonidine have been recorded in up to 48% of patients. In fact, chronic treatments with this drug lead to local adverse reactions like blepharoconjunctivitis, and follicular conjunctivitis, as well as systemic ones such as headache, fatigue, and sedation. Armisen *et al.* [23] diagnosed allergic contact dermatitis due to apraclonidine in one patient by patch testing and hypothesized that intermediate metabolites of this agent resulting from oxidization were responsible for sensitization.

Silvestre *et al.* [24] obtained positive results to patch tests with eye drops and apraclonidine 10%, but not 0.25%, 0.5%, or 1% in a 59-year-old man who had suffered conjunctivitis in his right eye and lichenified dry eczema of his lower eyelid and cheek in the past two years. Therefore, to confirm allergy to apraclonidine, it had been necessary to test at a higher concentration than that in the eye drops. This could be due to the presence of irritants, such as benzalkonium chloride, among the excipients that facilitate penetration of the allergen. It is also possible that apraclonidine itself is not the allergen, but rather an oxidation product [23].

Patients with delayed hypersensitivity to apraclonidine can still use other α -1-adrenergic eye drops, such as those based on brimonidine or clonidine, because these do not seem to cross-react with apraclonidine. [25, 26].

β -BLOCKERS

Betaxolol, carteolol, levobetaxolol, levobunolol, metipranolol, and timolol are used to treat certain types of glau-

coma. They seem to work by reducing the production of fluid in the eye and consequently its pressure.

Timolol, a nonselective β -blocker, is the most commonly used antiglaucoma medication and for this reason the one which is most often implicated in adverse reactions. This drug represents the standard to which other agents are compared in terms of efficacy, side effects, and costs.

Use of β -blockers can be associated with the exacerbation of asthma, congestive heart failure, heart block, and, rarely, with suddenly death [27].

After topical application, stinging, pruritus, and follicular conjunctivitis can occur; in some cases, contact dermatitis to these drugs has also been observed.

Most of the time, complete regression of ocular and cutaneous reactions occurs with discontinuation of the drops.

Girardin *et al.* [28] described the case of a 70-year-old woman who reported a 6-month history of pruriginous eruption. She had been affected since 1989 by open-angle glaucoma and had been treated with timolol 0.25% eye drops. The eruption consisted of papular lesions located on the arms, the back of the neck, and the back, consistent with prurigo. Histological examination revealed a dermal lymphocytic infiltration compatible with prurigo. There was no improvement after one month of topical corticosteroid, while the eruption cleared completely within a month after timolol had been withdrawn. This observation suggests a new general cutaneous side effect of β -blocker eye drops, namely prurigo. In fact, the chronology of clinical events in this case implicates timolol, although cutaneous tests were negative. Other allergic hypersensitivity reactions to this drug have been diagnosed by patch testing at concentrations ranging from 0.25% to 5.0% [29]. On the other hand, Katz [30] noted that the majority of conjunctival reactions to pharmaceutical preparations with timolol were not caused by the substance itself, but by the preservative, which usually is 0.01% benzalkonium chlorhydrate.

With regard to befunolol, there are cases of allergic contact dermatitis confirmed by patch testing [29, 31-34]. Specifically, Aoki [31] evaluated by patch tests 49 patients with contact dermatitis associated with eye drops; only in 3 cases dermatitis was due to befunolol, while in the others it was due to either a vehicle ingredient or benzalkonium chloride. Giordano-Labadie *et al.* [32] studied a subject who had developed chronic eczema during therapy with 3 different β -blockers – timolol, befunolol, and carteolol – administered in sequence. Patch testing with these drugs produced negative results. Therefore, it was hypothesized that the eczema had been caused by a sensitization to a common hapten, an aldehyde produced by drug degradation. Allergic contact dermatitis diagnosed by patch testing with the culprit β -blocker (betaxolol, levobunolol, carteolol, befunolol, and metipranolol) has been observed in single cases [35, 36]. In particular, O'Donnel and Foulds [35] observed a patient who had developed a contact allergy after years of exposure to 0.5% timolol. When these drops were replaced with betaxolol 0.5%, the eyelid dermatitis initially improved, but reoccurred months later. Betaxolol was replaced by 2% metipranolol, to which the patient had not previously been exposed, but contact dermatitis recurred again.

Quiralte *et al.* [36] reported a case of carteolol allergic dermatitis with extensive cross-reactivity to other topical β -blockers. Patch tests were positive to carteolol and timolol, as well as to levobunolol, a β -blocker never previously used by the patient.

Nino *et al.* [33] described the case of a 68-year-old woman with contact allergy after many years of befunolol or timolol exposure. Patch tests showed a cross-reactivity to carteolol.

Corazza *et al.* [34] proposed that the cross-reactivity among timolol, levobunolol, befunolol, betaxolol, and carteolol was caused by a common lateral aliphatic chain that conditions affinity to the receptor. Girardin *et al.* [28] hypothesized that the lateral aliphatic chain could be the antigenic determinant.

CARBONIC ANHYDRASE INHIBITORS

Dorzolamide is an inhibitor of the human carbonic anhydrase isoenzyme for topical glaucoma therapy [37]. Strahman *et al.* [38] performed a study comparing dorzolamide and β -blockers in 313 patients with glaucoma. During the monotherapy phase with dorzolamide, 4% of them developed conjunctivitis, 3% eyelid inflammation, and 3% itching eyes; such patients did not undergo patch testing.

Cases of contact dermatitis associated with this drug have been reported [39, 40-42]. Aalto-Korte [39] described 2 cases of allergic contact dermatitis due to a 0.5% solution of dorzolamide confirmed by patch tests. Shimada *et al.* [40] diagnosed the first Japanese case of allergic contact dermatitis due to dorzolamide on the basis of positive patch tests. In this case, stripping the horny layer of the skin prior to patch testing contributed to eliciting the reaction to the test agent. Mancuso *et al.* [41] reported a case of severe erythema, edema, and exudation of the eyelids and upper cheeks, with conjunctival hyperemia associated with dorzolamide therapy. Patch testing with this drug produced a positive reaction. A recent study by Linares Mata *et al.* [42] reported 2 cases of allergic contact dermatitis due to dorzolamide, diagnosed by both the scarified patch-test technique and a conjunctival provocation test.

PROSTAGLANDIN ANALOGS

Latanoprost is a topical eye medication used to reduce pressure inside the eye. It is used to treat eye conditions, including glaucoma and ocular hypertension, in which increased pressure can lead to a gradual loss of vision.

Jerstad *et al.* [43] reported a patch-test positivity to 0.005% latanoprost solution in an 85-year-old man with a history of tearing, red eyes, and pruriginous, edematous eyelid eczema associated with latanoprost therapy.

ANTIBIOTICS

After antiglaucoma drugs, antibiotics are the compounds most involved in hypersensitivity reactions to eye drops. All antibiotic classes may cause such reactions, but aminoglycosides, polypeptides, and sulfonamides are the main culprits.

Aminoglycosides

Among antibiotics, aminoglycosides contained in ophthalmic products currently predominate as the cause of contact conjunctivitis and blepharitis [44]. Cross-reactivity among them has been reported [45-48]; it is correlated with the deoxystreptamine ring B, common to all compounds, except streptomycin [46].

In spite of its frequent use, hypersensitivity reactions to tobramycin are rare [49, 50]. Recently, a case of conjunctivitis and blepharitis was observed in a 59-year-old non-atopic woman after several days of treatment with TobradexTM (tobramycin and dexamethasone) and atropine eye drops [51]. Patch tests were carried out with the European standard series (True TestTM, ALK-Abelló, Madrid, Spain), TobradexTM and its individual constituents (tobramycin sulphate 0.3% pet. and dexamethasone 0.1% pet.), atropine, TimoptolTM 0.5% (another kind of eye drops used by the patient), as well as with excipients (chlorhexidine, thimerosal, benzalkonium chloride). The only positive response was found for tobramycin sulphate at 96 hours. Skin prick tests with eye drops were also performed, with negative results.

Allergic contact dermatitis due to gentamicin is also rare in patients with eyelid dermatitis [52-54]. A 55-year-old non-atopic housewife presented a 3-week history of pruriginous, erythematous, scaly plaques on the eyelids, and a subsequent periorbital involvement developed 24 hours after starting treatment with Colircusi GentamicinaTM eye drops [55]. Patch tests were carried out with the GEIDC (Grupo Español Investigacion Dermatitit de Contacto) standard series, a medicament series (Chemotechnique), tobramycin (previously used by the patient), and Colircusi GentamicinaTM eye drops and its components. Positive reactions were obtained to Colircusi GentamicinaTM eye drops, gentamicin 20% pet., and kanamycin 10% pet., to which the patient had apparently not been previously exposed. A neomycin patch test was instead negative. These findings suggest cross-reactivity between gentamicin and kanamycin because of some structural similarity, but not with neomycin [56]. A single case of gentamicin hypersensitivity has been described, a 50-year-old man who developed erythema and edema of his eyelids and the periorbital area, as well as conjunctivitis 24 hours after starting to take two kinds of eye drops: Colircusi GentadexaTM (containing gentamicin) and MaxitrolTM (containing neomycin) [57]. Skin prick tests and immediate-reading intradermal tests with gentamicin sulphate (at 1 and 5 mg/ml) were negative, as well as an intramuscular challenge test up to an 80-mg dose of this drug. However, 48 hours later the patient exhibited erythema, infiltration, and vesicles on his forearm at the site of the intradermal test with gentamicin at 5 mg/ml. Neither ocular and systemic symptoms nor skin lesions at the site of the intramuscular injection appeared in the days following the challenge. The patient was then patch tested with the standard series (True TestTM, including neomycin sulphate) and with gentamicin sulphate (80 mg/ml aq.), showing a positive reaction only to the latter. This case is unusual in at least two aspects: the lack of cross-reactivity between gentamicin and neomycin, and the tolerance of systemic exposure to gentamicin in a patient with contact sensitivity to the same drug.

A systemic reaction to sisomicin has been described in a 32-year-old woman with a corneal allograft in the right eye, who developed an itchy maculopapular rash on the neck, the right popliteal fossa, and then on the chest, as well as an erythema of the right periorbital area 2 days after the first application of sisomicin eye drops [58]. A provocation test was performed one month later, when she was free of any symptoms; within 24 hours from the first application, a reaction similar to the previous one appeared. Patch tests were performed with sisomicin eye drops, other antibiotics, and benzalkonium chloride. A wheal reaction to variously diluted preparations of sisomicin was observed at 60 minutes after application, and a papuloerythematous reaction was observed 48 hours later. Similar results were observed with gentamicin sulphate, but not with other antibiotics, such as bacampicillin hydrochloride, erythromycin lactobionate, minocycline hydrochloride, and cefaclor, or benzalkonium chloride.

Polypeptides

Allergy to rifamycin seems to be rare. A few cases of contact dermatitis have been reported [59-63], while, to the best of our knowledge, there is only one report of a systemic reaction after application of eye drops containing rifamycin. A 36-year-old non-atopic woman had developed intense ocular pruritus and eyelid angioedema immediately following the administration of rifamycin on the fourth day of treatment [64]. Twenty-four hours later she had suffered a generalized urticaria that gradually disappeared upon discontinuing the eye drops. Four weeks earlier, she had used eye drops containing rifamycin for 6 days because of acute conjunctivitis. Skin prick tests with rifamycin (1 mg/ml) and rifampicin (2 mg/ml), to which the patient had never been exposed, were positive to both compounds, suggesting a cross-reactivity.

AN ERYTHEMA MULTIFORME

Sulfonamides

With regard to sulfonamide antibiotics that developed in an 8-year-old boy after topical administration of sodium sulfacetamide for conjunctivitis has been reported [65]. He experienced fever, eyelid swelling, purulent conjunctivitis associated with central corneal epithelial defects, and a maculopapular rash, which over the next few days progressed from papules to bullae, also involving his chest and back. Ulcerated lesions were also present on his lips and oral and pharyngeal mucosal surfaces. However, allergologic tests were not performed.

Vancomycin

Hypersensitivity to systemic vancomycin has been reported, but, to our knowledge, there is only one case of a hypersensitivity reaction to a topical compound. A 76-year-old non-atopic man with chronic endophthalmitis caused by *Propionibacterium acnes* suffered from progressive pruritus, soreness, burning, photophobia, and tearing in his left eye 3 days after completing 2 weeks of treatment with 5% vancomycin eye drops [66]. A severe periorbital erosive rash and swelling of the left eyelid were also noted. The patient's symptoms responded well to systemic corticosteroids, anti-

histamines, and topical corticosteroid treatment, resolving within 3 days after discontinuing vancomycin eye drops and starting the anti-reactive therapy. An allergologic examination was performed through skin and patch tests. Intradermal injections with 0.005% and 5% vancomycin, reconstituted with sterile water, were positive at immediate (15 minutes) and delayed (48 hours) readings. Patch tests at 0.005% and 5% concentrations of vancomycin were positive after 48 hours.

ANTIVIRALS

Adverse cutaneous reactions following the topical administration of antiviral drugs have rarely been observed. They are mostly mild and transitory skin eruptions; however, systemic manifestations of varying intensity have also occurred. Information concerning this aspect of antiviral therapy is sparse and scattered throughout the medical literature. A review of the available data identified 15 agents, including acyclovir, imiquimod, podophyllin, podofilox, cidofovir, penciclovir, vidarabine, idoxuridine, trifluridine, tromantadine, lamivudine, interferon (IFN), fomivirsen, foscarnet, and ganciclovir [67]. We have selected only a few representative cases.

Acyclovir

Contact dermatitis due to acyclovir seems to be an unusual reaction, since there are few reports in the literature. Valsecchi *et al.* [68] described a 52-year-old woman who experienced local erythema, edema, and vesicles with itching 10 days after the use of a cream containing acyclovir (ZoviraxTM) on her left thigh. She was patch tested with the GIRDCA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali) standard series, ZoviraxTM, acyclovir 1%, 3%, 5% pet., and the excipients, showing positive results to ZoviraxTM and acyclovir at all the different concentrations.

IFN- β

The only case of allergic contact dermatitis following the use of eye drops containing IFN- β (FroneTM) was observed in a 57-year-old painter who had suffered facial swelling, erythema, and vesicle formation [69]. Patch tests with the GIRDCA standard series showed positive reactions to some substances without any apparent relevance. The patient was then patch tested with FroneTM eye drops, showing positive reactions even after a 1:32 dilution. Negative results were instead obtained when each excipient was tested separately, as well as when patch tests were performed with IFN- α , IFN- γ , and a preparation in which the FroneTM IFN- β was inhibited by an anti-IFN- β antibody.

Idoxuridine and Trifluoridine

Idoxuridine allergic contact dermatitis has been described in at least 7 studies [70-76]. Relatively few cases showed positive reactions when patch tested with this drug; whereas many appeared to be due to the delivery vehicle components, including propylene glycol and dimethylsulfoxide [76].

Allergic contact dermatitis to trifluoridine eye drops has, instead, a very low incidence; in fact, only 2 cases have been reported. A 70-year-old male had a 3-month history of eczema of his left eyelid, which had been treated with various

eye drops [77]. He was patch tested with the Spanish standard series, topical medicament series, and his own ophthalmic products, showing a positive result only to Viomidin™ eye drops. Each component of this product was then patch tested with positivity to trifluoridine at 5 and 10% pet. Cirkel and van Ketel [78] described a patient sensitized to both idoxuridine and trifluoridine, pointing out the sensitizing properties of trifluormethylized trifluoridine and the likely cross-reactivity between this compound and idoxuridine. Interestingly, Amon *et al.* [70] observed cross-reactivity among this agent and other brominated and chlorinated, but not fluorinated, pyrimidine analogues.

NSAIDs

NSAIDs contained in eye drops may also cause hypersensitivity reactions, mainly respiratory ones in subjects with chronic asthma. However, in most studies, allergologic tests have not been performed.

A 79-year-old woman was treated after lens surgery with indomethacin eye drops and an ophthalmic solution containing polymyxin-B, neomycin, and dexamethasone [79]. One month later, she suffered a severe bronchospasm that required intubation and ventilation. During hospitalization, when her symptoms improved, the previous ophthalmic therapy was re-instituted; one hour after the administration of indomethacin eye drops, the patient had increasing respiratory distress, nausea, and diaphoresis.

Asthma exacerbations have been described in 2 women with longstanding asthma and nasal polyposis after a 3-week treatment with topical diclofenac for ocular redness and dull pain in one of them [80] and following the first administration of ketorolac prescribed for allergic conjunctivitis, in the other [81]. The latter also reported a history of bronchospasm after aspirin ingestion.

Cutaneous reactions to NSAID eye drops have also been reported. A 70-year-old woman, with a history of contact dermatitis from unidentified topical NSAIDs, developed an itchy erythema and edema of her eyelids, without conjunctivitis, 2 weeks after beginning treatment with various eye drops, including diclofenac sodium (Dichlod™), prednisolone acetate, sodium cromoglycate, and pranopfen [82]. She was patch tested with these eye drops and other NSAID preparations, displaying positive responses to Dichlod™, diclofenac sodium 2% pet., Inteban™ cream (1% indomethacin), and indomethacin 2% pet.

ANESTHETICS

Local anesthetics can provoke adverse idiosyncratic, cardiovascular, and allergic hypersensitivity reactions, the last ones being extremely rare.

A 60-year-old woman developed eczematous dermatitis of the eyelids after administration of ophthalmic anesthetic drops before laser surgery [83]. Patch testing was performed with the NACDRG (North American Contact Dermatitis Research Group) allergens, a topical anesthetic tray, and the anesthetic agents to which the patient had been exposed, showing a positive response to benzocaine 5% pet. (toward which she denied exposure), as well as to proparacaine and tetracaine 0.5%, which were contained in her eye drops. The

same authors also described chronic finger dermatitis in an ophthalmologist sensitized to topical anesthetic proparacaine. Despite discontinuance of proparacaine and its substitution with a patch-test-negative agent, tetracaine, his hand dermatitis persisted. Follow-up patch testing documented that a contact allergy to tetracaine, as well as to thiuram, had developed. These cases suggest a cross-reactivity among related local anesthetics, although concomitant sensitizations are also possible.

ANTIALLERGIC DRUGS

Antiallergic drugs contained in eye drops, in particular antihistamines, cromones, and amlexanox, may cause hypersensitivity reactions.

A 30-year-old woman, with a grass pollen allergy, suffered bilateral conjunctivitis and eyelid dermatitis for 4 months [84]. She was patch tested with the GIRDCA standard series and the ophthalmic products that she was using, showing positive reactions to nickel sulphate 5% pet., paraphenyldiamine 1% pet., and Tetramil™, eye drops containing tetrazoline chloride (sympathomimetic), and pheniramine maleate (H1-receptor antagonist). Further patch testing with the individual constituents of Tetramil™ and other antihistamines revealed positive reactions to pheniramine maleate and alkylamine derivatives (dexchlorpheniramine, chlorpheniramine, and diphenhydramine).

A 32-year-old woman, who used soft contact lenses, suffered severe, itchy, erythematous periorbital dermatitis, which spread to her cheeks, a few weeks after beginning treatment with Cusicrom™, eye drops containing sodium cromoglycate [85]. Patch testing was performed with the GEIDC standard series, a cosmetic series (Chemotechnique), a lens-cleaning solution (Boston-Cronoptica™), Cusicrom™ and its individual components [sodium cromoglycate, ethylenediaminetetraacetic acid (EDTA), Tween 80, and benzalkonium chloride], showing positive results to thimerosal, Cusicrom™, and Boston-Cronoptica™, and negative ones to the other reagents, including sodium cromoglycate at 1% aq. and pet. Instead, a positive result was found when sodium cromoglycate 1% was tested with benzalkonium chloride 0.1% pet., indicating a compound effect [86]. This case suggests that patch testing sometimes requires subtle variations in allergen concentrations and vehicles to obtain the right conditions for reaching epidermal antigen-presenting cells [87].

A 19-year-old man, with perennial conjunctivitis, presented ocular pruritus, hyperemia, chemosis of the conjunctiva, ocular redness, lacrimation, and eyelid edema several days after beginning treatment with Naaxia™, eye drops containing *N*-acetyl-aspartyl glutamic acid (NAAGA) [88]. Patch testing was carried out with the True Test™, some eye drops that he had previously used, and Naaxia™ and its individual components, showing positive results to Naaxia™ and NAAGA 1% pet.

Numerous cases of contact dermatitis due to amlexanox eye drops (Elics™) have been reported. In particular, Yamashita and Kawashima [89] described 3 cases of erythema and edema of the eyelids after administration of this drug; patch tests with Elics™ were positive in all patients. Amlexanox at concentrations ranging from 0.01 to 1.0% pet. was positive

in 2 cases (in one of which amlexanox was also tested at 1.0% aq., showing a reaction stronger than that observed with amlexanox pet.), while in the third one positive reactions were obtained only when amlexanox 0.25% was combined with methyl-*p*-hydroxybenzoate 0.026% aq. or propyl-*p*-hydroxybenzoate 0.014% aq.

OTHER

ϵ -Aminocaproic Acid

ϵ -Aminocaproic acid is a potent synthetic fibrolysin, widely used to control various hemorrhagic disorders. In Japan, it has also been included in some topical medicaments and cosmetics, eye drops, gargles, skin fresheners, soap, and toothpaste. Contact dermatitis to ϵ -aminocaproic acid is rare. Miyamoto and Okajima [90] described a subject with contact dermatitis due to eye drops containing ϵ -aminocaproic acid, who presented positive responses after 2 and 3 days of patch testing with eye drops and ϵ -aminocaproic acid 1.0% pet.

Penicillamine

Penicillamine administered topically as eye drops is used to prevent corneal fibrosis after chemical traumas. A 65-year-old painter developed erythema, edema, and vesicles on the eyelids and surrounding skin 6 weeks after starting treatment with 3 eye drops containing, respectively, penicillamine and chloramphenicol, atropine, and dexamethasone and vitamin C [91]. Patch testing with the European standard series, the Belgian Contact Dermatitis Group pharmaceutical series, and the patient's own eye drops showed positive reactions to penicillamine 0.15 M aq., benzoic acid 5% pet., and atropine 1% sal. Furthermore, because penicillamine is an important haptenic determinant in penicillin allergy [92], a patch test with penicillin 100,000 IU/g pet. was performed, but resulted negative.

N-Acetylcysteine

N-acetylcysteine is a mucolytic agent and, in combination with hypromellose eye drops, is commonly used to alleviate the chronic soreness associated with dry eyes. A 30-year-old woman with lifelong atopic eczema had a 10-year history of periorbital eczema associated with severe atopic keratoconjunctivitis and keratoconus; her treatment consisted of fluorometholone and sodium cromoglycate eye drops, in addition to hypromellose and N-acetylcysteine drops as tear replacement [93]. She was patch tested with an extended European standard series, facial series, medicament series, ophthalmic series including 1% ethylenediamine tetraacetate and 0.05% phenylmercuric acetate, and her own eye drops, showing positive results to preservative-free N-acetylcysteine eye drops 10% aq., phenylmercuric acetate, fragrance mix, and balsam of Peru.

Bismuth

Bismuth is used topically for bacteriostasis. A 33-year-old woman with a history of atopic hand eczema and allergic rhinitis presented an exacerbation of her periorbital dermatitis after treatment with Noviform™, bibrocathol-containing eye drops, which she had used previously [94]. She was patch tested with the European standard series, Noviform™,

and the components of bibrocathol (bismuth oxide and tetrabromocatechol), with positive results for formaldehyde, potassium dichromate, Noviform™, and bismuth oxide 5% pet.

Papain

Papain, a proteolytic enzyme obtained from papaya, is widely used in the chemical, food, and pharmaceutical industries. Chymopapain, a substance cross-reacting with papain, is used for chemonucleolysis. An IgE-mediated hypersensitivity to this enzyme has been reported in a 31-year-old woman who presented a 7-month history of chronic ocular pruritus, tearing, and episodic periorbital angioedema [95]. She used a commercial contact soft-lens-cleansing solution prepared dissolving a tablet of papain in a saline solution preserved with thimerosal and edetate disodium, experiencing the same symptoms each time. Prick tests performed with chemically untreated and heat-inactivated papain and chymopapain reagents were all positive at a 1 mg/ml concentration; prick-test titration with phenylmethylsulfonylfluoride-inactivated chymopapain showed a positive response at a 0.01 mg/ml concentration; furthermore, a positive reaction to a 1 mg/ml of sterile phosphate-buffered saline (PBS) solution of the soft-lens papain tablet was detected by prick testing. Control prick tests with the commercially preserved saline diluent solution and PBS were negative. Serum-specific IgE for both papain and chymopapain were detected by a modified RAST (radioallergosorbent testing assay).

Rubidium Iodide

Rubidium iodide is used in ophthalmic products to retard or prevent the formation of cataracts. A severe dermatitis of the face, eyelids, and periorbital areas, caused by eye drops (Polijodurato™) for the treatment of cataracts, has been described in a 70-year-old man [96]. Patch tests with the GIRDCA standard series, and Polijodurato™ and its individual constituents revealed positive reactions to wool alcohols and rubidium iodide 1% pet., but not to Polijodurato™.

Hyaluronidase

Hyaluronidase is an enzyme that depolymerizes the polysaccharide hyaluronic acid in the extracellular matrix of connective tissue, increasing the spread of locally injected anesthetics and improving the efficacy and speed of nerve blocks. An anaphylactic reaction to hyaluronidase has been reported. A 67-year-old woman initially developed gross chemosis and periorbital edema and then hypertension, sweat, nausea, and incontinence after administration of a local anesthetic consisting of prilocaine with octapressin and Hyalase™ (hyaluronidase) for a cataract operation [97]. She was patch tested with the European standard series, an eye drop series, and the materials used during the operation, showing a positive, but not significant reaction to phenylmercuric acetate. Prick tests performed with the materials of the operation produced a positive response to Hyalase™.

PRESERVATIVES

Allergic hypersensitivity reactions to preservatives are much less common than toxic ones, accounting for only

about 10% of all ocular adverse reactions. However, the potential allergenicity of preservatives in topical ophthalmic medications, though rare, should not be underestimated, as they may cause complications like conjunctival scarring and prolongation of symptoms during treatment. The main preservatives involved in allergic contact reactions are thimerosal, chlorhexidine, benzalkonium chloride, sorbic acid, phenylmercuric nitrate, polyquate, and parabens [98].

Thimerosal is the most allergenic preservative: the incidence of hypersensitivity ranges from 6.5% to 8% among individuals routinely screened for contact allergy in the USA, and reaches even 10% among soft-lens wearers; in other countries, this incidence in healthy subjects varies from 1.3% to 26%. This world-wide sensitization to thimerosal, found even in infants, has been explained as an iatrogenic consequence of mandatory parenteral vaccinations. Contact dermatitis to thimerosal is, however, exceedingly rare and most positive patch-test reactions to this preservative are clinically insignificant, except in ophthalmic patients. Tosti and Tosti [99] reported 36 patients with thimerosal-induced follicular allergic contact conjunctivitis, 18 of whom had been using thimerosal-containing eye drops, whereas 13 used soft contact lenses and became sensitized to their own thimerosal-containing lens solution. Patch tests were performed with the ICDRG (International Contact Dermatitis Research Group) standard series (Hermal-Trolab), and the eye drops or the soft contact lens solutions used by the patients and their single constituents, whenever available. All 36 patients showed a positive patch test reaction to thimerosal (0.1% pet.) (Hermal-Trolab), while only 1 of them reacted to an ophthalmic product (Visuglican™ eye drops). A case of underestimated contact allergy to thimerosal has been described in a 26-year-old man who suffered from a 2-year history of repeated episodes of dermatitis, swelling of his eyelids, and burning eyes treated with various eye drops, with a partial resolution [100]. His conjunctivitis completely resolved when the patient stopped working with a milling cutter, but reappeared after he started a different job at the same company. Suspecting an occupational allergy, he was patch tested with the European standard series, a disinfectant and preservative series, a base preparation and emollient series, a drug series, a mechanical workers' series, and different thimerosal-containing eye drops. A patch-test positivity was found to *p*-phenylenediamine, benzoyl peroxide, thimerosal, phenylmercuric borate, and thimerosal-containing eye drops often used by the patient. Phenylmercuric borate hypersensitivity was interpreted as a consequence of a cross-reactivity with thimerosal, because of the presence of a mercury compound in both allergens.

CONCLUSIONS

Hypersensitivity reactions, mainly contact dermatitis, to ophthalmic products are frequently reported and sometimes constitute a complex problem. Identifying the culprit allergen in such cases can be difficult. Multiple reviews, case series, and single case reports have been published on diagnostic strategies for ophthalmic contact dermatitis, and several ophthalmic trays have been suggested to date, but we are still far from standardization [44]. As far as contact dermatitis is concerned, patch testing remains the first step in diag-

nosing an allergy to ophthalmic products, even though its results are often negative. For this reason, strategies have been proposed to improve diagnostic work-up sensitivity. Admittedly, the very low concentration of allergens in commercial products could be insufficient to elicit an allergenic reaction on the back, and the anatomical and physiological properties of the eyelid skin, sometimes previously damaged by dermatitis, may entail a lower threshold of allergy-induction in comparison with the thick healthy skin on the back. Therefore, scratching and stripping the skin of the back in order to favor a higher percutaneous absorption could be a second step after conventional patch tests. Corazza and Virgili [101] also suggest to pre-treat the skin of the back with sodium lauryl sulphate (an anionic surface-active agent) before performing patch tests; this agent is capable of damaging the skin without systemic toxicity, allowing allergen penetration, and consequently increasing patch-test sensitivity. If no positive results are obtained, provocation tests should be performed [54]. Furthermore, chemical stability should be determined to obtain reproducible and reliable results and more controls in order to assess irritancy should be performed for certain compounds that have not thoroughly been tested.

ABBREVIATIONS

aq	= Aqueous
COX	= Cyclooxygenase
EDTA	= Ethylenediaminetetraacetic acid
g	= Gram
GEIDC	= Grupo Español Investigacion Dermatitis de Contacto
GIRDCA	= Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali
ICDRG	= International Contact Dermatitis Research Group
IFN	= Interferon
IgE	= Immunoglobulin E
IU	= International unit
LLT	= Lymphocyte transformation test
M	= Mole
mg	= Milligram
ml	= Milliliter
NAAGA	= <i>N</i> -acetyl-aspartyl glutamic acid
NACDRG	= North American Contact Dermatitis Research Group
NSAID	= Nonsteroidal anti-inflammatory drug
PBS	= Phosphate-buffered saline
pet	= Petrolatum
RAST	= Radioallergosorbent testing
sal	= Saline

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