

# Allergic reaction to topical eyedrops

Christophe Baudouin

## Purpose of review

To examine recently published papers dealing with drug-induced allergic reactions. As allergy is only one possible mechanism, this review was extended to all reports or studies describing allergic, inflammatory or toxic effects related to eyedrops since 2004.

## Recent findings

These studies were first classified into clinical reports or surveys, experimental works and biological studies showing drug-induced effects on the ocular surface or eyelids. Studies aimed at determining the role of preservatives or comparing preservative-free and preserved eyedrops were further analysed separately.

## Summary

Reports on allergic or toxic reactions of eyedrops are published repeatedly. The reports raising the most important issues are those concerning antiglaucoma drugs. They consistently describe inflammatory reactions at the conjunctival level, with strong evidence that preservative is a major source of toxicity for the ocular surface.

## Keywords

allergy, benzalkonium chloride, drugs, eyedrops, glaucoma, preservative, toxicity

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Departments of Ophthalmology, Quinze-Vingts National Ophthalmology Hospital, Paris, and Ambroise Paré Hospital, APHP, Boulogne, Paris-Ouest School of Medicine, University of Versailles, Paris, France; and INSERM U598, Cordeliers Biomedical Institute, University of Paris 5, Paris, France

Correspondence to Christophe Baudouin, Quinze-Vingts Hospital, 28 rue de Charenton, 75012 Paris, France  
Tel: +33 1 40 02 13 01; fax: +33 1 40 02 13 99;  
e-mail: baudouin@quinze-vingts.fr

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## Introduction

There is now a large amount of evidence from experimental and clinical studies that the long-term use of topical drugs may induce ocular surface changes, causing ocular discomfort upon instillation, tear film instability, conjunctival inflammation [1], subconjunctival fibrosis [2], conjunctival epithelium apoptosis, corneal surface impairment, and a potential risk of the failure of further glaucoma surgery [3]. Subclinical inflammation has also been described, with significant infiltration of the conjunctival epithelium and substantia propria by inflammatory cells [4,5] in patients receiving antiglaucoma treatments for long periods of time. However, the mechanisms involved, i.e. allergic, toxic or inflammatory, as well as the respective roles of the active compound and the preservative in inducing toxic or pro-inflammatory effects of ophthalmic solutions is still being debated. The most frequently used preservative, benzalkonium chloride, has widely demonstrated its toxic effects in laboratory [6], experimental [7] and clinical studies [8]. As a quaternary ammonium, this compound is much more than an excipient, and has been shown to cause directly or has shown some evidence of causing tear film instability, the loss of goblet cells, conjunctival squamous metaplasia and apoptosis [9], disruption of the corneal epithelium barrier, severe loss of endothelial cells if accidentally introduced in the anterior chamber [10], and even blood–aqueous barrier disruption in the early phase of pseudophakia, leading to the new concept of pseudophakic preservative maculopathy [11].

During the past year several papers were published dealing with eyedrop toxicity or allergy, most of them confirming the large role, even though not exclusive, of preservatives in inducing adverse events on the ocular surface. Some reports were focused on allergic manifestations, others were aimed at investigating ocular surface inflammation with more sophisticated tools and techniques, in relation to eyedrops and their preservatives. This review is divided into three parts: (1) clinical reports on drug-induced ocular manifestations; (2) biological studies; and (3) comparative studies aimed at determining the role of the preservative.

## Clinical manifestations of drug-induced ocular surface side-effects

Ocular drugs may induce a wide variety of reactions. Allergy is the most prominent reaction from a clinical point of view, but is in fact far less frequent than chronic

subclinical inflammatory changes induced throughout the ocular surface by the repeated use of eyedrops.

### **Drug-related allergic reactions**

Drug-induced allergy remains in most clinical trials a relatively rare situation, occurring in a few percent of patients, mostly in the early course of treatment. A study aimed at evaluating latanoprost eyedrops as second-line therapy showed ocular allergic reactions in only 1.5% of patients [12]. Other cases were reported with various eyedrops, including tobramycin eyedrops [13], or brimonidine tartrate [14,15]. In the first study reporting brimonidine side-effects [14], anterior uveitis and conjunctivitis were found associated with the long-term use of this eyedrop. The second study [15] was aimed at evaluating clinical factors associated with brimonidine allergy. The authors found high rates of ocular allergy (13.5% of patients) with a mean time of occurrence after the beginning of treatment of approximately 15 days. This may not encounter later allergic manifestations, as often observed in clinical practice, especially at the palpebral level. The only risk factor found in that report was a history of previous allergy to eyedrops.

Other clinical manifestations may also be related to drug toxicity, without the occurrence of allergic reactions. Corneal punctuate staining was therefore evaluated in healthy individuals after treatment for 5 days with either latanoprost, travoprost or bimatoprost. The authors did not find any significant differences between the three groups [16]. Another study in healthy volunteers compared the tolerance of two ophthalmic solutions of new generation fluoroquinolones, preserved gatifloxacin, and unpreserved moxifloxacin [17]. Despite the absence of preservative in the latter solution, the tolerance of moxifloxacin was lower than that of gatifloxacin. This effect could be attributed at least partly to prostaglandin release in the anterior chamber after moxifloxacin treatment. The studies therefore illustrate the importance of discriminating early, acute allergic reactions from often more delayed toxic and non-specific inflammatory mechanisms that may require some time to occur or result from indirect inflammatory mechanisms. The low rate of true allergy should therefore never let these hidden toxic/inflammatory reactions be neglected.

### **Periocular dermatitis**

In addition to allergic conjunctivitis, which rarely corresponds to type I hypersensitivity, the most frequent drug-induced allergic reaction is a type IV delayed cell-mediated hypersensitivity. This may explain why many reactions occur at the eyelid level, causing allergic blepharitis, which is often difficult to differentiate from other causes of eyelid inflammation or contact dermatitis. Several cases were therefore reported, with antibiotics [13], or antiglaucoma drugs, even with an

atypical lichenoid eruption [18]. A large series of patients with periorbital dermatitis was tested on medications in a Department of Dermatology [19]. The authors showed true allergic reactions to preservatives or active compounds in two-thirds of patients with periorbital dermatitis. They also emphasized the need for testing with patch tests not only standard antigens or chemical compounds but also eyedrops brought by the patients as they may contain atypical compounds or combinations.

### **Drug-induced ocular pseudopemphigoid**

Pseudopemphigoid is a very severe toxic scarring reaction of the ocular surface, similar to that found in cicatricial ocular pemphigoid or Stevens–Johnson syndrome of immunological origin. In many aspects it resembles cicatricial ocular pemphigoid, but all pathological investigations usually fail to show any auto-antibodies in the conjunctiva. The evolution is usually severe, with complete corneal scarring after a chronic phase of inflammation, with a poor visual prognosis, especially in bilateral forms. A new case of drug-induced ocular pseudopemphigoid, fortunately unilateral, was recently reported [20], and reminds us that this complication is related to eyedrops and may occur after several years of treatment.

### **Failure of filtration surgery**

Without this level of gravity, subconjunctival scarring has been reported in the past, as the long-term use of anti-glaucoma eyedrops was shown to be associated with significant foreshortening of the inferior conjunctival fornix, in relation to subepithelial fibrosis [2]. It has also been widely suspected that the failure of filtration surgery might be related to drug-induced fibrosis and to subclinical inflammatory reactions caused by topical medications [3]. Flach [21] in 2004 critically analysed the published studies supporting this hypothesis. Most of the studies demonstrated the presence of inflammatory reactions in the conjunctiva of patients undergoing further glaucoma surgery. Because of the wide variety of study designs, mostly retrospective uncontrolled case series, and the disparity of topical treatments, the author could not draw definitive conclusions from the literature. However, all previous pathological studies cited in the paper were consistent with the fact that the conjunctiva of glaucoma patients was abnormally inflammatory after years of treatments, which could nevertheless possibly influence further surgery, increasing the risk of fibrosis and filtration failure.

### **Biological or experimental assessment of drug-induced corneal or conjunctival changes**

In addition to clinical manifestations, a variety of biological or pathological techniques may be used to assess ocular surface changes caused by eyedrops.

### Corneal barrier disruption

In healthy volunteers exposed to either preserved or unpreserved 0.5% timolol, corneal epithelial barrier function was studied using a technique of fluorophotometry [22]. Both drugs disrupted the epithelial barrier function, but to a significantly greater extent in the preservative-containing group. This suggests that toxic effects may only be visible at the cellular level with functional or morphological impairment.

### Conjunctival biopsies

Cellular involvement, either in terms of toxic reactions or chemotactism of inflammatory or fibroblastic cells, may often only be evaluated using ex-vivo specimens. The most relevant, although aggressive and not routinely usable, are conjunctival biopsies. Recent reports confirmed previous studies showing, in patients treated over the long term with topical glaucoma medications, squamous metaplasia, inflammation and subconjunctival fibrosis [23•]. Apoptosis related to drug use was also recognized as being increased in the conjunctival epithelium of glaucoma patients receiving topical drugs, whatever the type, number and duration of treatments [24••]. Increased apoptosis rates in ocular surface epithelia is in agreement with previous in-vitro studies showing in conjunctival cell lines the pro-apoptotic effects of several drugs and preservatives [6].

On the other hand, a study dealing with another clinical issue, the mechanism of conjunctival hyperemia after treatment with bimatoprost [25], failed to show in conjunctival biopsies any difference in terms of vascular congestion or subconjunctival inflammation, compared with control normal conjunctivas.

### Tear samples

Although ocular surface specimens require complex techniques for evaluations of inflammation or toxicity, tear samples are easily available for such investigations, but are rarely used. Manni *et al.* [26••] performed a crossover study comparing patients receiving preserved and unpreserved timolol, with tear IL-1 $\beta$  in tears as the primary criterion. Only the preserved timolol group showed a significant increase in this major proinflammatory cytokine, together with a significant decrease in the break-up time. This again favours a pro-inflammatory effect of antiglaucoma drugs, at least partly under the influence of the preservative.

### Impression cytology specimens

In contrast to conjunctival biopsy, impression cytology is a widely used, non-traumatic, almost painless method for collecting conjunctival cells. Epithelial cells, goblet cells and inflammatory cells may be differentiated according to immunostaining procedures, standard cytological techniques or, after extraction from the collection membrane,

using a technique of flow cytometry, allowing the measurement of the expression of membrane or cytoplasmic markers related to inflammation or apoptosis. Different studies have thus been performed and published in 2004, using the validated technique of flow cytometry in impression cytology specimens in glaucoma patients receiving topical treatments over the long term. Two studies from the same group [27••,28•], who previously developed this technique and demonstrated the overexpression of HLA-DR class II antigens in ocular surface diseases, showed that this marker was strongly expressed in the conjunctival epithelium of glaucoma patients.

The first study [27••] investigated patients who had received preserved timolol or the prostaglandin analogue latanoprost for at least one year. Results from impression cytology specimens demonstrated that latanoprost induced a lower conjunctival inflammation than did preserved beta-blocker. Moreover, the study also investigated MUC5AC-positive cells, as a witness for mucin secretion or goblet cell density. Even though the number of MUC5AC-positive cells was lower after treatment with latanoprost than with unpreserved timolol, it remained significantly higher with latanoprost than with preserved timolol treatment. Altogether, these results demonstrated that the effects of latanoprost upon conjunctival cells, as evaluated by an increase in inflammatory marker expression and a decrease in mucin production, were less substantial than expected for a prostaglandin analogue, and lower than the toxic or inflammatory levels caused by prolonged treatments with preserved timolol.

The other study based on the same technique investigated interleukin expression by conjunctival epithelial cells [28•]. IL-6, IL-8 and IL-10 were overexpressed in all glaucoma groups, compared with normal eyes, whatever the type of treatment received. This would suggest that interleukin expression by conjunctival cells is dependent upon immune mechanisms and pathways other than those influencing adhesion molecules and class II antigens, which were mainly overexpressed in eyes receiving preserved drugs. Interleukin expression could be hypothesized to be a global reaction to toxic drugs administered for long periods of time to the ocular surface. However, the conjunctival profiles of HLA-DR and the three interleukins seemed to differ, and further studies will be necessary in order to obtain a better understanding of the roles of immune markers, chemotactic, proinflammatory or inhibitory cytokines in conjunctival reactions to eyedrops.

### The role of preservatives

From all clinical, experimental or ex-vivo studies, it appears that the preservative may be largely responsible for allergic, toxic or inflammatory reactions induced or

favoured by topical drugs. Even in the past year, several studies have been aimed at discriminating between the respective roles of preservative and active compounds.

### Experimental studies

An experimental study was conducted in rabbits using in-vivo confocal microscopy in order to evaluate the toxicity to the ocular surface of five fluoroquinolones. Epithelial thickness was found to be significantly decreased with all preparations, except with moxifloxacin, the only preparation in a preservative-free formulation [29]. Similarly, Noecker *et al.* [30] compared the effects on the ocular surface of a series of antiglaucoma drugs in rabbits. They found, using scanning electron microscopy and light microscopy, less damage in the cornea and lower inflammatory infiltrates in the conjunctiva with those drugs containing the least preservative concentrations, especially brimonidine purite and bimatoprost. The study by Pisella *et al.* [27<sup>••</sup>] also comprised an in-vitro part demonstrating the toxicity of benzalkonium chloride, the neutral effect of unpreserved timolol, and the interesting finding that the commercial solution of latanoprost was less toxic than its corresponding concentration of benzalkonium used as control. This would indicate a partial protective effect of latanoprost that deserves further studies on prostaglandin analogues.

### Clinical studies

A survey performed on 3090 patients with allergic conjunctivitis by 507 general practitioners [31<sup>•</sup>], compared the symptoms experienced by patients upon the instillation of either preserved or unpreserved anti-allergic eyedrops. Interestingly, 2712 patients were using unpreserved drugs, which shows the habit of practitioners towards preservative use for allergic conjunctivitis in France where the study was conducted. Compliance and the frequency of adverse reactions were significantly higher in the preservative-free group, as the proportion of patients with at least one symptom was as high as 89% in the preserved group, versus only 24% in the preservative-free group. The survey is in agreement with a previous similarly conducted study on 4107 glaucoma patients [32], showing significantly less discomfort upon instillation, symptoms between instillation, and eyelid, corneal and conjunctival signs in patients receiving unpreserved drugs. These events occurred in a dose-dependent manner and decreased after moving to unpreserved drugs or reducing the amount of preservative-containing eyedrops.

### Biological criteria

Few reports in the past addressed the issue of alterations at the ocular surface induced by topical drugs, especially in glaucoma, a disease in which ocular surface epithelia are probably normal at the onset of treatment. The technique of flow cytometry in impression cytology

specimens was used to evaluate the effects of preserved or preservative-free timolol and the prostaglandin analogue latanoprost on the conjunctival epithelium, by investigating HLA-DR, interstitial cell adhesion molecule 1, and MUC5AC-related mucin production [27<sup>••</sup>]. The study demonstrated that the beta-blocker, when preserved with benzalkonium chloride, induced significantly higher inflammatory levels in the conjunctival epithelium than did its preservative-free counterpart, which by itself did not stimulate a significant expression of the inflammatory marker compared with normal untreated eyes. The study was not prospective, because of the long duration probably required for topical treatments to induce inflammatory reactions. However, it was designed as a case-control study, using an objective, highly reliable tool in order to analyse in a masked manner conjunctival inflammatory reactions.

In the study a significant decrease in MUC5AC-positive cells was also found in glaucoma patients. In those treated with preserved antiglaucoma drugs, the subclinical inflammation was associated with a highly significant decrease in mucin-expressing cells compared with normal eyes and patients receiving preservative-free timolol. The impairment of goblet cell density and mucin production by the conjunctival epithelium could therefore at least partly be explained by the chronic inflammatory reaction of the ocular surface induced by the preservative. However, it could also be hypothesized that benzalkonium chloride itself may trigger a direct toxicity on conjunctival goblet cells, as previously demonstrated in the conjunctival epithelium.

In addition, some of the above-mentioned studies showing inflammation or toxicity related to eyedrops consistently concluded that unpreserved eyedrops were safer than preserved eyedrops, with less IL-1 $\beta$  [26<sup>••</sup>], better tear stability and corneal barrier function [22], lower apoptosis rates in conjunctival cells [24<sup>••</sup>] when using unpreserved solutions and high levels of inflammatory infiltrates with preserved drugs [23<sup>•</sup>].

### Conclusion

Drug-induced adverse effects are far from being restricted only to allergic reactions, and the long-term use of eyedrops has consistently been reported to induce inflammatory ocular surface changes, causing progressive ocular discomfort upon instillation, tear film instability, corneal surface impairment, and the potential risk of the failure of further glaucoma surgery. Reports and experimental studies are repeatedly and consistently focusing on the large part played by benzalkonium chloride in these reactions. Care should therefore be taken to avoid preservatives in long-term use as much as possible, and to limit their concentration, as their toxicity is dose and time dependent, or to develop new non-toxic preservatives,

capable of reducing allergic reactions and improving ocular surface tolerance over the long term.

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