Abstract: Long-term use of topical drugs has clearly been shown to induce toxic immunopathological changes in the ocular surface. Lacunae exist in the knowledge regarding the respective roles of active compounds and preservatives. The preservatives used in topical multidose ophthalmic preparations are responsible for a considerable compromise of ocular surface. In chronic diseases like glaucoma where long-term medical treatment is the mainstay of therapy, drug induced surface toxicity is a matter of concern. Toxicity is dose-dependent and concentration-dependent and generally varies according to the overall health of the eye. For glaucoma patients thought to be at risk for ocular surface damage, choosing medications with either low levels of Benzalkonium chloride, alternative preservatives such as Stabilized oxychloro complex, or preservative-free preparations may reduce side effects and increase tolerability of the therapy. This review, based on a literature search using Medline, attempts to present a comprehensive picture of the effect of various antiglaucoma medications and their preservatives on the health of ocular surface.

Keywords: Glaucoma therapy, side effects, hypersensitivity, dermatitis, preservatives.

INTRODUCTION

Topical ophthalmic medications are required by the US Food and Drug Administration to contain a preservative so that patients are provided with microbe free medication. Despite good tolerance and apparent safety, topical medications have recently been noted to induce long-term ocular surface changes which may often cause damage to conjunctival and corneal cells. Chronic topical medical therapy has a deleterious effect on the surgical outcome due to chronic inflammation. There have been several reports of the adverse effects of prolonged topical therapy, partly due to the preservatives associated with the preservatives in the formulation and partly due to the drug itself. This review, based on an extensive literature search using Medline with the PubMed search engine, attempts to amalgamate the effects of all classes of antiglaucoma medication on ocular surface, so as to provide the reader with a comprehensive overview of the problem. Well-documented individual patient reports and patient series of ocular surface manifestations of long-term use of topical antiglaucoma drugs in English literature were reviewed. References within these articles were also obtained for review.

Preservatives

Preservatives are antiseptic substances formulated with the principal compound of the eyedrops to prevent microbial contamination within multiple-use containers. Prolonged use has been associated with toxic and inflammatory changes of the ocular surface. Preservatives have come under the scrutiny of research studies over the years for their potential to disrupt the protective tear film and ocular surface cells.

Benzalkonium Chloride

Benzalkonium chloride (BAC) – a quaternary ammonium cationic detergent is the most commonly used preservative in topical ophthalmic preparations. It is used in a concentration ranging from 0.02 to 0.004%. It interacts with high affinity with membrane proteins and may change the ionic resistance of the cornea by intercalating into the cellular membrane. The detergent action of BAC can also enhance the effectiveness of some drugs by increasing their penetration and delivery to the cornea. This is achieved through BAC’s ability to increase the spacing between epithelial cells. During the first 48 hours following BAC application, epithelial tissues show the highest concentration, and the half-time for the elimination from the corneal and conjunctival epithelium is approximately 20 hours. Benzalkonium chloride can accumulate and remain in ocular tissues for relatively lengthy periods and may induce cell toxicity and/or death in a dose-dependent manner. Three
types of mechanisms have been described for BAC: these are detergent effects, causing loss of tear film stability, toxic effects to the corneal and conjunctival epithelium, and immunological reactions. Lemp et al reported a case of toxic endotheliopathy with BAC and this was proved clinically and histopathologically.

With use of the Wong-Kilbourne derivative Chang conjunctival cell line, Baudin et al compared in vitro ocular toxicity of travoprost 0.004% containing 0.015% benzalkonium chloride (BAC), travoprost Z 0.004%, a new formulation without BAC, and latanoprost 0.005% containing 0.02% BAC. Assessment of cell viability and membrane integrity revealed a significant effect by latanoprost with BAK or BAK alone but no effect by travoprost Z without BAK or buffer alone (P < 0.0001). Latanoprost with BAK, travoprost with BAK, and BAK alone were cytotoxic in Chang conjunctival cells, whereas no cytotoxicity was observed in cells exposed to travoprost Z without BAK or in cells treated with buffer (P < 0.0001).

**Purite**

Purite – a stabilized oxychloro complex (SOC) – is an alternative preservative to BAC and is used in brimonidine purite 0.1% and 0.15% and purite-preserved artificial tears. SOC consists of an equilibrium mixture of 99.5% chlorite, 0.5% chlorate and trace amounts of chlorine dioxide. It oxidizes unsaturated lipids and glutathione in the cell and has proven antibacterial efficacy. When SOC is instilled into the eye, it is converted into natural tear components: sodium and chloride ions, oxygen and water. In a rabbit model by Noecker et al brimonidine purite produced less conjunctival infiltration than latanoprost, timolol or bimatoprost.

**Sof Zia™ Preservative System**

The SofZia™ preservative system is a proprietary ionic buffer system consisting of zinc, borate, propylene glycol and sorbitol, and designed to be dissipated by the ocular tear film. BAC-free travoprost (Travoprost Z ophthalmic solution) is as safe and effective in lowering IOP as the commercially available travoprost 0.004%.

Kahook and Noecker compared the changes in the number of goblet cells after chronic exposure to latanoprost preserved with 0.02% benzalkonium chloride (BAK) eyedrops (Xalatan; Pfizer, NY, USA), travoprost preserved with sofZia eyedrops (Travatan Z; Alcon, Fort Worth, TX, USA), or preservative-free artificial tears (Refresh Plus; Allergan, Irvine, CA, USA), in white rabbits. They found that the number of goblet cells in the latanoprost with BAK group was significantly lower than the other two groups (P = 0.0001). There was no statistically significant difference in goblet cell numbers between the travoprost with sofZia and preservative-free artificial tear group (P = 0.24).

They also noted significantly more corneal epithelial damage with latanoprost than travoprost with sofZia (P = 0.0001).

**Others**

These include less commonly used ophthalmic preservatives as benzododecinium bromide (BDD), cetrimide (CET), EDTA, phenylmercuric nitrate, thimerosal (THI), methyl parahydroxybenzoate (MPHB), chlorobutanol (CLB), chlorhexidine digluconate (CHX), sorbic acid, chlorobutanol, sodium perborate, and polyhexamethylene biguanide hydrochloride (PHBG), which are used in ophthalmic preparations and contact-lens care solutions.

**Effects on Ocular Surface**

Toxicity is dose-dependent and concentration-dependent and generally varies according to the overall health of the eye. The deleterious effects of preservatives on the ocular surface are of particular concern for patients with chronic conditions, such as glaucoma or keratoconjunctivitis sicca. Repeated applications of multiple medications can lead to significant accumulation of preservative in ocular tissue and increased risk of ocular surface damage.

**Tear Film Changes**

A single drop of 0.01% benzalkonium chloride can break the superficial lipid layers of the tear film into numerous oil droplets which are made soluble. This is because benzalkonium chloride can insert into the lipid monolayer of the tear surface and disrupt it by detergent action. Repeated blinking does not restore the lipid layer for sometime.

Preservatives also destabilize the tear film indirectly by decreasing the density of goblet cells in the conjunctival
epithelium. Yalvac et al showed in their study that the chronic application of 0.05% timolol maleate and 0.1% dipivefrin with BAC as preservative damaged the ocular surface by decreasing the aqueous layer production rate and impairing the mucous layer of tear film. Another study by Herreras et al concluded that chronic application of a commercial preparation of timolol maleate 0.5% damaged the ocular surface by decreasing the aqueous layer production rate and impairing the quantity and quality of the mucous layer of the tear film.

**Conjunctival Changes**

The conjunctiva is known to be the principal target of the toxic effects of topical ophthalmic preparations. Besides the principal ingredient, the preservatives prove to play a major role in these adverse events through an indirect effect on the lacrimal gland or a direct toxic effect on the epithelial cells. Preservatives, according to their nature induce both a cytotoxicity and allergic reaction. Hong et al demonstrated that various topical IOP-lowering medications induced a significant degree of squamous metaplasia, especially in fixed-combination therapy, and that the prolonged use of these drugs might change the conjunctival surface.

**Squamous Metaplasia**

A small number of studies have indicated that topical medical treatment increases the number of fibroblasts and inflammatory cells in the conjunctival substantia propria, decreases the number of epithelial goblet cells, and induces a degree of epithelial goblet cells and induces a degree of epithelial metaplasia with ultrastructural change. Hong et al demonstrated that various topical IOP-lowering medications induced a significant degree of squamous metaplasia, especially in fixed-combination therapy, and that the prolonged use of these agents might change the conjunctival surface. Guenoun et al studied the inflammatory and toxic profiles of three topical prostaglandins and commented that BAC might be the major factor responsible for long-term ocular surface reactions in these preparations.

**Subepithelial Fibrosis**

Histopathologically, this is characterized by subepithelial fibrosis without acantholysis. Pfister and Burstein found that certain miotics such as pilocarpine 2% or echothiophate 0.25% produced cellular changes including moderate loss of microvilli and wrinkling of plasma membranes and premature desquamation.

Langerhans cells are potent antigen-presenting cells of the conjunctival epithelium and subepithelial chorion. They are the first line of immune cells in contact with the topically applied drugs, and they migrate into the subepithelial space and activate lymphocytes and other cells, such as macrophages, which recruit by themselves additional inflammatory cells, lymphocytes, or mast cells. Such cascade activation maintains a constant inflammatory state and may result in the recruitment of fibroblasts and, therefore, subconjunctival fibrosis.

In an experimental study on rabbits by Mietz et al a slight increase in thickness of subepithelial collagen of conjunctiva was present in the group treated with medication and preservative compared to medication alone.

**Ocular Cicatricial Pemphigoid**

Butt Z et al describe eight cases of presumed drug-induced cicatrizing conjunctival changes simulating ocular cicatricial pemphigoid (OCP), following the chronic use of topical glaucoma medication. It is unclear whether topical glaucoma therapy promotes OCP or accelerates the emergence in a predisposed individual. Also unilateral pemphigoid has been documented related to topical therapy for unilateral glaucoma which is rare otherwise. A condition resembling ocular cicatrical pemphigoid has been described in association with epinephrine and pilocarpine.

**Follicular Conjunctivitis**

There are many reports about the acute follicular conjunctivitis effects of topical echothiophate, pilocarpine and dipivefrin hydrochloride. Hence it is recommended that the conjunctiva be examined regularly for early changes which may progress causing severe discomfort.

**Corneal Changes**

Corneal complications attributed to the preservatives in topical ophthalmic preparations have been discussed in cases pertaining to contact-lens wearers, dry eye syndrome and glaucoma therapy. Whenever a preserved ophthalmic solution is used for a chronic disease, superficial punctuate keratitis is often noted. Subtle signs of ocular toxicity, such as
superficial punctuate keratitis, indicate chronic cell injury that can have long-term preservatives. In the cornea, application of preservatives induces reduction in cell proliferation and viability.16,34,35 Due to corneal epithelial dysfunction the cells when exposed to stress are unable to maintain strong adhesion to matrix of stroma. Berdy et al used scanning electron microscopy to compare the effect of two preservative-free artificial tears with that of a 0.02% BAC solution on the corneal epithelium of rabbit eyes.36 In this study, rabbit corneas subjected to mild use (2 drops every 30 minutes for 4 hours) of the 0.02% BAC solution showed loss of microvilli, increased number of epithelial holes, and loss of hexagonal shape. Corneas treated with an exaggerated BAC dosing regimen (2 drops every 3 minutes for 1 hour) exhibited diffuse cell peeling, retraction of cell membrane borders, destruction of microvilli, and loss of the superficial layer of the corneal epithelium. Conversely, the damage induced by the artificial tear solutions was mild, and was significantly less than the damage induced by the exaggerated dosing regimen of BAC. Becquet et al reported toxic effects of preserved solutions induced corneal damage, and limbal and conjunctival infiltration by immunocompetent cells. In glaucoma, the rate of inflammatory reaction could play a role in its evolution, by disrupting ultrastructure and extracellular matrix composition of the trabeculum.37 Cytotoxic effects of three preservatives – BAC, chlorobutanol and thiomersal were studied by Gasset et al in rabbit eyes and found that only BAC caused significant damage to all the cellular components of the cornea.1 The studies showing the effects of BAC exposure have yielded statistically significant differences on the ocular surface with the use of preservatives. It is unclear how much of these effects are translated in living human eye with intact tearing and nasolacrimal drainage systems. Studies employing clinical concentrations and dosing for BAC containing eyedrops have found that the morphology of epithelial cells, when analyzed by scanning laser ophthalmoscopy, is not significantly different from that observed with the use of preservative-free eyedrops.33

Changes in the Tenon’s Capsule
Increase in tenon’s capsule fibroblasts was found in rabbit’s eye treated with preparations of metipranolol and pilocarpine with preservatives BAC and cetrimonium chloride respectively.26 Sherwood et al studied the morphologic differences in conjunctiva and tenon’s capsule between patients who had received prior medical therapy and those who had not and found a significant increase in the number of macrophages, lymphocytes and mast cells in the group treated with topical medications. Fibroblasts also were more prominent in the deeper conjunctiva and tenon’s capsule in the topical medication group.40

It is possible that these morphologic responses are the determinant factors for the success of a filtering bleb. For glaucoma patients thought to be at risk for ocular surface damage, choosing medications with either low levels of BAC, alternative preservatives such as SOC, or preservative-free preparations may reduce side effects and increase the tolerability of the therapy.

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 (Fig. 1). Several cases have been reported, with antiglaucoma drugs, even with an atypical lichenoid eruption.41 A review of the literature has identified 10 agents causing contact dermatitis among topically administered drugs for glaucoma.

Atypical Band Keratopathy
Kennedy et al reported on 18 patients with atypical band keratopathy who were treated with miotics for glaucoma.38 They hypothesized that phenylmercuric nitrate had a significant role to play and this was supported by other reports of mercury toxicity.39

Fig. 1: Periocular dermatitis
These agents include β-blockers (timolol, befunolol, betaxolol, levobunolol, carteolol, metipranolol), a carbonic anhydrase inhibitor (dorzolamide), a parasympathomimetic (pilocarpine), and sympathomimetics (dipivefrin, apraclonidine). Patch testing has been documented in certain individuals as well as cross sensitization and reactivity.42

**Drugs**

**Sympathomimetics**


Several Studies have documented the conjunctival changes induced by timolol and pilocarpine, and epinephrine compounds.16,43 In a study by Burstein et al, the Schirmer’s test and tear break up time was significantly less in patients treated with Timolol or Dipivefrin as compared to controls, due to compromised mucin layer.3 Increase in tenon capsule fibroblast was found in rabbit’s eye treated with preparations of metipranolol (BAC +) and pilocarpine (cetrimonium chloride).26 There are many reports about the acute follicular conjunctivitis effects of topical dipivefrin hydrochloride and apraclonidine.32,44 Timolol inhibits the corneal epithelial migration as reported by Liu et al in rabbit organ culture system.45

Propranolol and practolol, the first few commercially available topical hypotensive drugs were withdrawn due to adverse reactions like corneal anesthesia, dry eye related problems, corneal ulcers and subconjunctival fibrosis.46-48 Phenyl mercuric nitrate, the preservative used in pilocarpine in the past, was found to cause atypical band keratopathy.38,39

**Prostaglandins**

Prostaglandin analogs have favorable safety profile and low systemic side effects but possess potential proinflammatory properties. *Ex vivo* and *in vitro* studies by Pisella et al demonstrated that BAC – containing Latanoprost exhibits higher proinflammatory and proapoptotic effects than does unpreserved timolol. Their results suggested a potential protective effect of the prostaglandin analogs against the toxicity of BAC in conjunctival cells.49 Latanoprost is shown to prevent excessive fibrous tissue formation, potentially through upregulation of MMP-3 and TIMP’s in the conjunctival epithelium.50 Liu et al have shown latanoprost to inhibit the corneal epithelial migration.45 Topical application of latanoprost to the cornea reduces the central corneal thickness, an effect that might result in underestimation of the level of the intraocular pressure as measured by appplanation tonometry.51 Guenoun et al have shown that due to low BAC concentration in bimatoprost the toxicity in experimental conditions was lower than Latanoprost and travoprost. They further hypothesized that prostanoids have a protective effect against BAC induced toxicity as lower adverse effects were noted even when a higher concentration of BAC was used.52

**Topical Carbonic Anhydrase Inhibitors**

Topical dorzolamide may cause a hypersensitivity reaction in the form of marginal keratitis.53 Dorzolamide, with a BAC concentration of 0.0075% has been shown to induce more corneal epithelial damage than either latanoprost or timolol, both of which contain higher levels of BAC. These findings suggest that dorzolamide-induced corneal damage may be secondary to low pH (5.6) and not solely to the preservative.10 Brinzolamide and dorzolamide have been associated with superficial punctate keratitis and corneal erosions.54

**Comparative Effect with Various Drugs**

In the evaluation of corneal damage in the study by Noecker et al,11 brimonidine purite® produced significantly less damage than the ocular hypotensive agents with higher concentrations of BAC—latanoprost (0.02% BAC), timolol (0.01% BAC), and dorzolamide (0.0075% BAC, P = 0.001). The corneal damage seen with brimonidine purite® was not significantly different from that associated with artificial tears. Bimatoprost, which contains the lowest BAC concentrations of the evaluated medications (0.005%), was also associated with significantly less damage than latanoprost, timolol, or dorzolamide (P = 0.002). Dorzolamide, on the contrary, with a BAC concentration of 0.0075%, induced more corneal epithelial damage than either latanoprost or timolol, both of which contain higher levels of BAC. These findings suggest that dorzolamide-induced corneal damage may be secondary to low pH (5.6) and not solely to the preservative.
Multidrug Therapy

Brandt et al while studying conjunctival metaplasia with impression cytology noted that triple therapy had significant metaplastic changes as compared to single or dual drug therapy. Ariturk et al have shown that a longer therapy period and especially triple medication use was associated with marked epithelial hyperplasia, keratinization and subepithelial lymphocyte infiltration.

Duration of Therapy

Previous therapy with topical medications for more than three years was associated with a significant increase in the number of pale cells (antigen presenting Langerhan cells whose increased count is an indicator of early inflammation) and subepithelial fibroblasts, macrophages, lymphocytes and mast cells in the study by Broadway et al. Similar findings have been reported by Schwab et al who reported that antiglaucoma medication use for greater than three years was associated with significant foreshortening of conjunctiva.

Longstaff et al conducted a study to identify potential risk factors for failure of pressure control following glaucoma triple procedure and found that the only significant adverse factor was cumulative years of preoperative topical therapy. The hazard ratio for this factor was 1.1 implying that the risk of failure doubled after 8 years of cumulative therapy.

Effect on Outcome of Filtration Surgery

The most common cause of filtering surgery failure is external scarring of the bleb from wound healing. Increased inflammation and proliferation of fibroblasts with the production of new collagen in the early postoperative period, and the presence of hypocellular fibrous tissue in the late postoperative period are characteristic of failed filtering procedures. The risk of bleb encapsulation after trabeculectomy may be enhanced by conjunctival inflammatory infiltration before surgery, as demonstrated by several studies, based on conjunctival biopsy specimens taken at the time of filtration surgery. Long-term therapy with topical antiglaucoma medications may increase filtering surgery failure by increasing inflammation and proliferation of fibroblasts. There occurs a wide range of conjunctival and Tenon’s capsule response to an apparently similar therapeutic insult. This range of response might explain why some trabeculectomies fail while others function.

Increase in tenon’s capsule fibroblasts was found in rabbit’s treated with preparations of metipranolol and pilocarpine with preservatives BAC and cetrimonium chloride respectively. Lavin et al found filtering surgery to be more successful in patients who instilled medication for an average duration of two weeks, as compared to patients treated for more than a year. They also noted that patients who had previous exposure to sympathomimetics were more likely to have failed trabeculectomies.

CONCLUSION

Compliance and the continuation of drug therapy are the cornerstones of treatment for a chronic disease as glaucoma. For medical treatment to be effective, the adverse drug reactions need to be minimal. Furthermore, a compromised ocular surface due to chronic inflammation has an adverse effect on the surgical outcome. Therefore, selection of ocular hypotensive drugs containing formulation components with low levels of cytotoxicity may reduce damage to the conjunctiva and cornea, especially over the course of chronic treatment.

REFERENCES


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“Small opportunities are often the beginning of great enterprises”.  
—Demosthenes