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REVIEW ARTICLE

BENZALKONIUM CHLORIDE: RE-EVALUATION OF ITS PHARMACEUTICAL STATUS

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ABSTRACT

The mainstay of treatment in a chronic disease like glaucoma is topical medications. Most of these medications need to be preserved with a preservative as mandated by the US FDA. Benzalkonium chloride (BAK) is the most widely employed preservative. It causes corneal and conjunctival damage and leads to various ocular surface disorders (OSD) which affect quality of life of the patients. The causality assessment of BAK has firmly established its role in the patho-physiology of OSD. This is further reinforced by many in vitro and in vivo studies. Chronic use of BAK challenges the basic concept of ocular therapeutics as it is bound to lead to the singular and quite predictable fate i.e. iatrogenic OSD over long term use. Hence, there is a need for newer preservatives or preservative free medications so that ocular surface health is not compromised in the long-term treatment of glaucoma.

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INTRODUCTION

Glaucoma is a slow and progressive degeneration of the retinal ganglion cells and optic nerve axons associated with visual dysfunction (Foster *et al*., 2002). The prevalence of glaucoma is increasing so rapidly that it is among the top two causes of blindness all over the world (http://www.who.int/ blindness/ causes/en/). As per the epidemiological statistical estimates, number of people with glaucoma worldwide will increase from 64 million to 76 million by 2020 (Tham, 2014; Quigley and Broman, 2006). To make the matter worse, blindness caused by glaucoma is irreversible if left untreated (Rotchford, 2005). The mainstay of treatment in glaucoma is medical with surgery being the last option. Topical ophthalmic antiglaucoma medications are the main component of medical treatment of glaucoma (Lee and Higginbotham, 2005). Various categories of topical antiglaucoma medications include prostaglandin analogs, beta blockers, cholinergic agents, adrenergic agonists and carbonic anhydrase inhibitors.

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Prostaglandin analogs are the most efficacious and convenient to use due to their once daily dosing. Moreover, they are also preferred due to their remarkable safety profile leading to better patient compliance (Lee and Higginbotham, 2005; Sambhara and Aref, 2014). These multidose topical medications must include a preservative so that they have a prolonged shelf life and minimal microbial contamination; thereby a relatively preserved potency and efficacy (Leung *et al*., 2008; Baudouin, 2008). The US FDA has made the use of preservatives in topical preparations mandatory (Food and Drug Administration, 2008). However, prolonged use of these "preservative conserved- topical medications" in a chronic disease like glaucoma leads to the development of ocular surface disease (OSD) (Kastelan *et al*., 2013). Ocular surface disorders have been documented in nearly 15 % of the geriatric group and in 48-59 % of patients on topical medications (Tokuda *et al*., 2015). Ocular surface disease is basically an umbrella term which encompasses both dry eye and non-dry diseases. The underlying pathophysiology in ocular surface disease is believed to be disruption of the tear film. Tear deficiency, tear film instability, irritation and inflammation leads to development of dry eye. Patient usually complains of discharge, irritation, dry eye sensation, foreign body sensation, grittiness, burning, poor or blurred vision

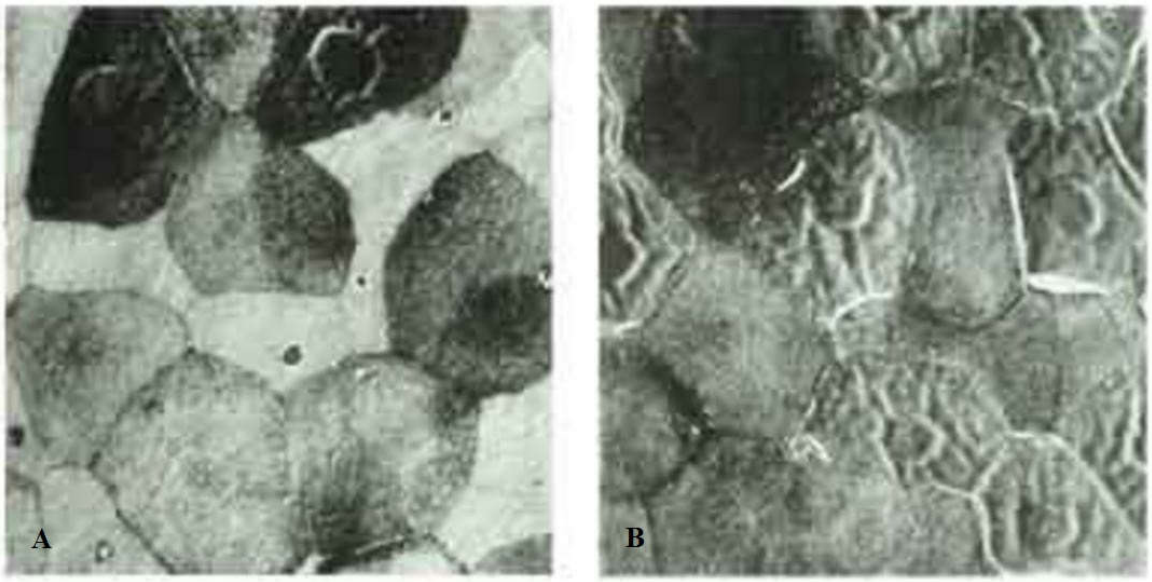

Figure 1(A). A scanning electron micrograph of rabbit corneal epithelium after mild dosing with 0.02% benzalkonium chloride. In Figure 1(B). After exaggerated dosing with 0.02% BAK, there is an increase in epithelial holes, a loss of peripheral microvilli and a noticeable wrinkling of surface cells. (Adapted and reproduced with permission) (Whitson, 2006)

Table 1. Various in vitro studies

In vitro Studies		
S. No.	Study findings	Conducted by
1.	The risk of toxicity to a human corneal epithelial cell was far less in the culture exposed to travoprost preserved without BAK than the culture exposed to latanoprost preserved with BAK.	Yee (2006)
2.	Higher concentration of BAK significantly reduced the mucin levels in immortalized human corneal epithelial cells.	Chung *et al*. (2006)
3.	Human conjunctiva-derived cells suffered significant cytotoxic effects when exposed to BAK-preserved latanoprost, BAK-preserved travoprost and BAK alone. It clearly implicated BAK to be underlying culprit.	Baudouin *et al*. (2007)
4.	The effect of preservatives on survival of human corneal endothelial cells showed that the survival was lower in cells exposed to BAK than in controls.	Ayaki *et al*. (2009)
5.	There was a direct link between the presence of BAK in anti-glaucoma eye drops and the likelihood of Human corneal endothelial cells (HCEC) toxicity.	Ayaki *et al*. (2010)
6.	The chances of survival were more in human corneal epithelial cells which were exposed to BAK-free travoprost than those which were exposed to travoprost with BAK.	Ammar *et al*. (2010)
7.	Hyperosmotic conditions were responsible for increased cytotoxicity of BAK. Also, BAK, owing to its tear disrupting action, promoted dry eye and tear hyperosmolarity. It resulted in a vicious cycle as BAK promoted the conditions which could lead to its own cytotoxicity.	Clouzeau *et al*. (2012)
8.	BAK-induced cytotoxicity was dose-dependent i.e. as dose of BAK increased, the likelihood of cytotoxicity increased as well.	Kim *et al*. (2013)
9.	Anti-allergic eye drops containing BAK as a preservative produced more cytotoxic effects.	Ana *et al*. (2014)
10.	There was a dose as well as time dependent negative correlation between the viability of human trabecular meshwork cells and BAK treatment.	Chang *et al*. (2015)

Table 2. Various in vivo (animal as well as clinical) studies

In vivo Studies		
S. No.	Study findings	Conducted by
1.	Topical preserved anti glaucoma preparations caused huge damage to the rabbit corneal endothelium.	Gasset *et al*. (1974)
2.	BAK preserved eye drops caused great damage to the ocular surface.	Yalvac *et al*. (1995)
3.	Rabbit corneas exposed to BAK-preserved latanoprost showed increased epithelial permeability, while those exposed to travoprost without BAK did not experience corneal toxicity.	McCarey *et al*. (2007)
4.	Improvement in OSD symptoms and better patient compliance in glaucoma patients who switched from BAK- preserved latanoprost to BAK-free travoprost.	Miyashiro *et al*. (2010)
5.	Preservative-free tafluprost was better tolerated than preserved latanoprost, while maintaining IOP.	Uusitalo *et al*. (2010)
6.	Preservative-free tafluprost 0.0015% was effective, well tolerated and safe.	Hommer *et al*. (2011)
7.	In newly diagnosed POAG patients, instillation of BAK-preserved travoprost led to tear film instability.	Tomic *et al*. (2013)
8.	BAK free eye drops were non inferior in lowering IOP and produced lesser adverse effects and lesser conjunctival hyperaemia than BAK-preserved latanoprost.	Rouland *et al*. (2013)
9.	BAK free latanoprost was as effective as latanoprost with BAK, and was more likely to maintain ocular surface health than latanoprost with BAK.	Kasai *et al*. (2013)
10.	Abnormal Tear film break up time (TBUT) was associated with BAK-containing eye drops, although this also occured with the use of preservative-free eye drops.	Norlina *et al*. (2015)

(The International dry eye work shop study group, 2007). Pathologically, there is goblet cell loss, macropannus and filamentary keratitis (O'Brien, 2007). Benzalkonium chloride (BAK) has been the favourite preservative of the ophthalmic industry. Its bags the top position in being an essential ingredient of topical antiglaucoma preparations (Freeman *et al*., 2009). It is a mixture of alkyl benzyl dimethylammonium chlorides of different alkyl chain lengths, containing even carbon numbers from C8 to C18, mostly C12 and C14. It is used in a concentration of 0.02 %- 0.004 % (Ophthalmic dosage forms, 2009). Out of the various commercially available preparations of prostaglandin analogs. latanoprost (Xalatan; Pfizer) has the highest concentration of BAK (0.02 %) (Pfizer, 2003) BAK is the main culprit behind the development of OSD. BAK is a detergent type of preservative. It disrupts the lipid component of the tear film. It gets inserted into the cellular membrane owing to its strong affinity for the membrane proteins. This further leads to a change in the ionic resistance of the membrane of cornea. It resides in the ocular tissues for a very long period of time (Actis and Rolle, 2014). BAK mainly causes activation of lipooxygenase enzyme and formation of various inflammatory mediators (Sachdeva *et al*., 2011). Toxic effects of BAK have already been demonstrated in many in vitro as well as in vivo models. Unfortunately filtration surgery which is the ultimate management option in glaucoma patients also fails when it is done after chronic use of preserved preparations (Chen *et al*., 2011). Non-quaternary ammonium compounds are documented to cause less oxidative stress as compared to BAK (Debbash *et al*., 2001). There are many evidences to consolidate the hazardous effects of BAK. These evidences are based on various in vitro and in vivo (animal as well as clinical) studies.

Alternative preservatives (Sachdeva *et al*., 2011; Bagnis *et al*., 2011; http://perso.numericable.fr/preservative-free/ English/ consequences-compare-preservatives.htm)

- Purite® is an oxidative type of preservative. After use, it gets converted to natural tear components following exposure to light. It has no adverse effect on epithelial cells in vitro or in vivo. It is also comparatively less disruptive to cellular integrity if compared with other preservatives. (Sachdeva *et al*., 2011)
- Sofzia® is another preservative. The components of Sofzia® are boric acid, propylene glycol, sorbitol and zinc chloride. It acts by causing oxidative damage and consequently death of organisms which lack the reactive oxygen species (ROS) scavenging enzymes like cytochrome oxidase and catalase, such as most species of bacteria. Human cells, however, have these enzymes and are thus spared.(Bagnis *et al*., 2011)
- Polyquad (polyquaternium-1) is a polycationic polymer. It is commonly used as a preservative in solution for contact lenses. It is currently used in eye drops and provides an excellent alternative to BAK. (http://perso.numericable.fr/ preservative-free/English/consequences-compare-preserva tives.htm)

Conclusion

The use of preservative in any multidose topical preparation is always needed as well as recommended. But it has been several decades since the use of BAK as a preservative was first challenged. Now its role in the pathophysiology of OSD is well established. As a result, BAK has earned the notorious nickname of being "controversial ophthalmic preservative (Chang *et al*., 2015)". The priorities are to be set beforehand by the concerned ophthalmologists and should be well defined. The aim of ocular pharmacology should be more focussed on the long term preservation of eyes rather than ocular medicines. Chronic use of BAK challenges the basic concept of ocular therapeutics as it is bound to lead to the singular and quite predictable fate i.e. iatrogenic OSD over long term use. Moreover, OSD affects the quality of life in glaucoma patients and also compromises their compliance and tolerability to medications as well. These factors (i.e. quality of life, patient compliance and tolerability) are important considerations in a chronic disease like glaucoma where long-term treatment is required. Hence, awareness of physician as well as pharmaceutical industry is crucial. Early diagnosis and management of OSD is the need of the hour. Although BAK has dominated as an unchallenged preservative for a long time, particularly in developing countries owing to its low cost; it is high time to reconsider and re-evaluate its pharmaceutical status as a preservative.

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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