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Preservatives in glaucoma medication

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ABSTRACT

Preservatives continue to be in widespread use in ophthalmic medications due to the convenience they provide, regulatory requirements and the higher cost of alternatives. Benzalkonium chloride (BAK) remains the most commonly used preservative but there is a trend towards the use of preservative-free (PF) drops for glaucoma, although at a higher price. An extensive body of literature explores BAK toxicity on ocular structures in animal and laboratory studies (in vitro and in vivo). Non-randomised controlled studies have provided some supporting evidence of its toxicity in patients, especially in those with pre-existing ocular surface disease (OSD) or on multiple medications. However, there have been very few randomised controlled trials that compare the same medication with and without BAK preservative. Several of these trials have never been published in any peer reviewed journals. Notwithstanding, those that have been published, have not demonstrated any clear benefits of the BAK-free formulations. Short duration and exclusion of those with OSD are limitations of these studies. There is a lack of evidence of clinically significant harm from a small number of BAK preserved drops in patients without OSD. This means that generally more expensive PF glaucoma medications should only be recommended for those on poly pharmacy or those with OSD but are not necessarily required for all patients.

INTRODUCTION

The use of preservatives extends the shelf-life of medications considerably. Patients would be able to administer their drops in a convenient and cost-effective way by allowing one large bottle of drops to last for a whole month. Their use has been a requirement in multidose containers by many regulatory authorities since the 1970s.¹ Benzalkonium chloride (BAK) has been used in ophthalmology since the 1940s. It is by far the most common preservative, found in approximately 70% of eye drops.^{2,3} It is used in different concentrations varied from 0.004% to 0.02%. It is a quaternary ammonium compound that acts as a detergent, lysing cell membranes and thus killing microorganisms. It is highly effective as a preservative. It was also initially thought that the detergent effect of BAK might be necessary for the penetration of the active ingredient.⁴

Other preservatives and available alternatives

Concern over the toxicity of BAK has led to other classes of preservatives being developed (table 1). These include polyquaternium-1 (Polyquad) which is a detergent, the oxidising preservatives such as Stabilised Oxylchloro Complex (SOC, trade name Purite) and Sodium perborate (GenAqua)

and the ionic buffered preservative SofZia. Additionally, advances in bottle design have created new dispensing mechanisms (such as COMOD or ABAK) that allow longer lasting preservative-free (PF) bottles. However, these are not widely available. Furthermore, there is a trend towards unit-dose preparations of glaucoma drops to eliminate the need for preservatives.⁵ Common preserved and PF glaucoma medications (drops) currently available in the UK are summarised in tables 2 and 3.

Search strategy

A 'PubMed' search was performed using the terms 'glaucoma medication' and 'preservative'. Randomised double-blind controlled clinical trials were sought within the results, of which only three comparing the same medication with and without preservative were selected. Other studies of interest are also discussed. We searched 'glaucoma' and 'preservative' terms on 'ClinicalTrial.gov' website in order to identify unpublished clinical trials.

Preservative toxicity

The laboratory and animal studies on the negative effects of BAK on the ocular structures have been the driving force against preservatives. Most of the literature concentrates on BAK as this is regarded as the most toxic and is the most commonly used. Other preservatives have been shown to exhibit less toxicity.^{6,7} In general, the antimicrobial activity of the preservative is inversely proportional to its compatibility with the ocular surface.⁶ Excipients (pharmacologically inactive substances acting as carriers for the active components), free radicals load and pH may also have an impact on the ocular surface. These parameter levels were found to be considerably variable between different glaucoma medications.⁸

BAK toxicity

BAK has been demonstrated to have detrimental effects on many ocular structures including the conjunctival tissue and corneal epithelium as well as the trabecular meshwork and lens epithelium.^{9,10}

Conjunctiva

Guenoun *et al* and several other studies found that at very low doses BAK induced proapoptotic effects on conjunctival epithelial cell lines.¹¹⁻¹⁴ Notably though these studies did not demonstrate apoptotic effects from the active pressure-lowering compounds. In human subjects, prolonged exposure to multiple preserved glaucoma medications have been shown to produce inflammatory changes in the subepithelial conjunctiva, although reversible on cessation of the medication. However,



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Table 1 Commonly used preservatives in eye drops

Compound	Class	Antimicrobial action	Trade name	Example
BAK	Quaternary ammonium	Detergent action dissolves cell walls and membranes	N/A	Lumigan, Xalatan, etc
Polyquaternium 1	Detergent	Acts on cell membranes	Polyquad	Tears Naturale II
SOC	Oxidising	Oxidation of intracellular lipids and glutathione	Purite	Alphagan P
Sodium perborate	Oxidising	Forms hydrogen peroxide, oxidising action similar to the above	GenAqua	Genteal
Borate, sorbitol, propylene glycol and zinc	Ionic buffer	Multiple	SofZia	Travatan Z

BAK, benzalkonium chloride; SOC, Stabilised Oxychloro Complex.

comparisons have not been made with patients on PF medications.^{15 16} Leal *et al*¹⁷ examined the histology of patients with hyperaemia from bimatoprost (BAK 0.005%). They concluded that it was not associated with inflammation, although this was after only 15–30 days use.

Cornea

Cell lines of three-dimensional corneal cells have shown similar apoptotic response to BAK, more so in superficial layers but in the deeper layers as well when apoptotic marker assays were used.¹⁸ However, other studies using the same three-dimensional model did not find any loss of cell viability.¹⁹ This highlights the difficulty of replicating studies using such models. In an animal model using in-vitro confocal microscopy, Liang found inflammatory infiltrates in the corneal epithelium, cellular swelling and desquamation from glaucoma medications, worst in those with BAK as a preservative.¹⁰

Trabecular meshwork

BAK is clearly toxic to trabecular meshwork cells. The laboratory studies have shown reduced cell numbers, growth and altered morphology^{20–22} and increased proapoptotic activity.²³ An accumulation of BAK has been found in the trabecular meshwork of patients treated chronically (5–10 years) with BAK preserved medications.²⁴ This has led to the hypothesis, yet unproven though, that chronic BAK exposure might worsen glaucoma.¹

Lens and other structures

BAK has been shown to strongly induce the expression of inflammatory mediators in lens epithelial cells²⁵ compared with latanoprost or timolol. The Blue Mountains Eye Study and Ocular Hypertension Treatment Study both suggested higher rates of cataract formation in those on antiglaucoma therapy.^{26 27} Miyake²⁸ conducted studies that suggested that BAK preserved drops prior to cataract surgery increased the risk of cystoid

Table 2 Common glaucoma preparations available in preserved formulation

Preserved drops				
Medication	Brand name	Drug concentration	Preservative	Preservative concentration
Prostaglandin analogues				
Latanoprost	Xalatan	50 µg/mL	Benzalkonium chloride	0.02%
Bimatoprost	Lumigan	100 and 300 µg/mL	Benzalkonium chloride	0.02%
Travoprost	Travatan	40 µg/mL	Polyquad	0.01%
Beta blockers				
Timolol	Timolol and Timolol LA	2.5 and 5 mg/mL,	Benzalkonium chloride	0.01%
Levobunolol	Betagan	5 mg/mL	Benzalkonium chloride	0.004%
Betaxolol	Betoptic	2.5 and 5 mg/mL	Benzalkonium chloride	0.01%
Alpha blockers				
Brimonidine	Alphagan	2 mg/mL	Benzalkonium chloride	0.005%
Apraclonidine	Iopidine	5 and 10 mg/mL	Benzalkonium chloride, propylene glycol	0.01%
Carbonic anhydrase inhibitors				
Brinzolamide	Azopt	10 mg/mL	Benzalkonium chloride, disodium edetate	0.01%
Dorzolamide	Trusopt	20 mg/mL	Benzalkonium chloride	0.0075%
Combinations				
latanoprost 50 µg/mL, timolol 5 mg/mL	Xalacom		Benzalkonium chloride	0.02%
Lumigan 300 µg/mL, timolol 5 mg/mL	Ganfort		Benzalkonium chloride	0.05%
Travatan 40 µg, timolol 5 mg/mL	DuoTrav		Polyquad	0.01%
Brinzolamide 10 mg/mL, timolol 5 mg/mL	Azarga		Benzalkonium chloride	0.1%
Dorzolamide 20 mg/mL, timolol 5 mg/mL	Cosopt		Benzalkonium chloride	0.0075%
Brimonidine 2 mg/mL, Timolol 5 mg/mL	Combigan		Benzalkonium chloride	0.05%
Brimonidine tartrate 2 mg/mL, Brinzolamide 10 mg/mL	Simbrinza		Benzalkonium chloride	0.03%

Source: British National Formulary 2017.

Table 3 Common glaucoma preparations available in non-preserved formulation

Non-preserved		
Name of medication	Brand name	Drug concentration
Prostaglandin analogues		
Latanoprost	Monopost	0.005%
Bimatoprost	Lumigan UD	0.03%
Tafluprost	Saflutan	0.015%
Beta blockers		
Timolol	Tiopex and Timoptol unit dose	0.1%, 0.25% and 0.5%
Carbonic anhydrase inhibitors		
Dorzolamide	Trusopt preservative free	2%
Combinations		
Bimatoprost/timolol	Ganfort UD	0.03%, 0.5%
Tafluprost/timolol	Taptiqom	0.015%, 0.5%
Dorzolamide/timolol	Cosopt preservative free	2%, 0.5%

Source: British National Formulary 2017.

macular oedema. At a molecular level, DNA damage has been noted from BAK exposure in a dose-dependent fashion.²⁹

Clinical studies

Clinically, the detergent properties of BAK can affect the lipid layer of the tear film, reducing tear breakup time (TBUT) and goblet cell numbers and mucin production are affected as well.^{30,31} Many clinical studies have illustrated an increased level of corneal staining, reduced TBUT and other markers of ocular surface disease (OSD) with BAK preserved medications.^{32–34} OSD, to quote Batra *et al*,³⁵ is an 'umbrella term that includes dry eye, lid disease, conjunctivitis and keratitis'. While there are validated scoring systems for OSD such as the Ocular Surface Disease Index (OSDI),³⁶ many studies used different subjective measures to evaluate the frequency and severity of OSD.

A French survey of over 4000 patients found those on PF drops had roughly half the symptoms and signs of OSD compared with those using preserved drops.³³ Additionally, they demonstrated a large reduction of symptoms and signs on reducing the dose of

preservatives or switching to PF. However, other clinical studies have found little or no corneal toxicity from various concentrations of BAK. A meta-analysis concluded that no significant difference in corneal staining occurred in patients that had twice the dose of BAK per day as others. Furthermore, BAK containing drops did not produce significant corneal toxicity in the vast majority of patients.³⁷

Published randomised controlled trials

Overall studies that suggest more frequent adverse effects on those individuals who are on preserved medications have not been double masked³⁸ or have not compared the same preserved and non-preserved medications.^{39,40} There have been a very few double masked randomised controlled clinical trials (RCTs) published which PF drops are directly compared with the same drop containing preservative. An analysis of bias using the Cochrane review process was done and the following three RCTs were assessed as low risk. Briefly the randomisation processes were described, the two different medications in each study were dispensed in identical bottles and the investigators and patients were masked as to the study medication. Outcome data short and longer term was close to complete for all patients with 96%–98% of patients completing the studies with results reported.

These studies are summarised in table 4.

Shedden *et al* reported in a double-masked study of 261 patients who were randomised 1:1 to either a PF combination of dorzolamide/timolol or one containing BAK at 0.0075% concentration.⁴¹ All patients had either ocular hypertension (OHT) or primary open-angle glaucoma (POAG). Efficacy was assessed by intraocular pressure (IOP) measurements done after a 3-week lead in on timolol alone and then at 2, 6 and 12 weeks after treatment with either PF or preserved dorzolamide/timolol combination. Tolerability was assessed by reported adverse events (AEs) by patients and objective clinical assessment. The efficacy of both preparations of dorzolamide/timolol was found to be equivalent at all time points. Overall both formulations were well tolerated. No statistical difference was found in terms of AEs between the two formulations. Furthermore, a similar percentage in each group had punctate epithelial erosions on examination (23.8% preserved vs 16.8% PF). Three patients

Table 4 Ocular adverse effects of preserved vs PF medications in RCTs

AEs	Sheddon		Day		Goldberg	
	PF	BAK	PF	BAK	PF	BAK
Overall %	Not reported	Not reported	Not reported	Not reported	33.1	33.7
Conjunctival hyperaemia	Not reported	Not reported	23.9	26.1	21.2	19.5
Mild	Not reported	Not reported	17.6	21	16.5	15.6
Moderate	Not reported	Not reported	6.3	4.4	4.0	3.9
Severe	Not reported	Not reported	0	0.7	0.7	0
Pruritus	Not reported	Not reported	4.0	4.1	4.3	1.8
Skin pigmentation	Not reported	Not reported	Not reported	Not reported	4	1.4
Dry eye	Not reported	Not reported	1.7	3.1	3.2	1.1
Punctate keratitis	16.8	23.8	3.0	3.1	2.9	2.5
Eye pain	Not reported	Not reported	Not reported	Not reported	2.5	1.8
Foreign body sensation	Not reported	Not reported	2.3	0.7	2.2	2.1
Eye irritation	16	21.5	Not reported	Not reported	2.2	1.8
Eyelash growth	Not reported	Not reported	Not reported	Not reported	1.4	2.8
Erythema	Not reported	Not reported	Not reported	Not reported	1.1	2.5
Discontinuation due to ocular AE (by patients)	4	3	2	3	4	9

AEs, adverse events; BAK, benzalkonium chloride; PF, preservative-free; RCT, randomised controlled trials.

in the BAK group and four in the PF group discontinued their medication due to adverse effects.

Day *et al* in a double-masked randomised clinical trial, compared bimatoprost 0.03% PF with bimatoprost 0.03% containing BAK at a concentration of 0.005%.⁴² They randomised just under 600 patients with OHT and various types of glaucoma. Those on other chronic ocular medication or with ocular surface findings were excluded, although hyperaemia was the only such finding which was specified. The duration of treatment was 12 weeks with evaluations at baseline, 2, 6 and 12 weeks. There was no statistically or clinically significant difference between the two formulations in terms of tolerability. Ocular AEs occurred in 32% of the PF group (two of whom stopped treatment) and 35% of the BAK group (three of whom stopped). Hyperaemia rate, pruritus and punctate keratitis were almost identical, although more severe staining was slightly more common in the BAK group at 6.8% vs 3.7% ($p=0.086$). Foreign body sensation occurred more in the PF group (seven patients, 2.3%) than in the BAK group, (two patients, 0.7%). The efficacy of medications was similar in both groups.

Goldberg *et al* compared bimatoprost 0.03%/timolol 0.5% PF with BAK (0.005%) preserved formulation.⁴³ Five hundred and sixty-one patients with either OHT or POAG were randomised. Those with chronic use of other ocular medication or with ocular surface findings (only hyperaemia or irritation were mentioned) were excluded. This was a double-masked RCT which was conducted for 12 weeks following a washout period of 4–28 days (depending on their medication). Safety was evaluated by self-reported adverse effects, slit lamp examination and grading of conjunctival hyperaemia based on the Oxford hyperaemia scoring system. Both formulations were safe and well tolerated. Treatment-related AEs (table 4) were reported in 28.8% in the PF group and 28.7% in the BAK group. Conjunctival hyperaemia was the most common AE which was usually mild. No significant difference was found between the two groups in terms of conjunctival hyperaemia, pruritus, dry eye, eye pain, eye lash growth and eyelid erythema. Skin hyperpigmentation was significantly more common in those on the PF formulation (4% vs 1.1%, $p=0.028$), a finding that was thought to be incidental.

Efficacy

In all three aforementioned studies, the IOP lowering effect of the PF medications was non-inferior to the preserved preparation, indicating that BAK is not required for adequate drug penetration, in line with other studies demonstrating equivalent efficacy between BAK preserved and PF glaucoma medications.⁴⁴

Unpublished randomised controlled trials

Several moderately sized RCT have been carried out comparing BAK preserved medications to those with alternative preservatives. Unpublished studies with reported results available are summarised in table 5.

However, no statistical analysis of the results had been attempted. It is not clear why these studies were not formally published. It could be speculated that it may have been due to the lack of clinically significant difference found between the medications being compared.

Patient satisfaction

Ultimately, glaucoma treatment can only be successful, if it is used by patients, thus compliance is a significant issue. Treatment satisfaction has been identified as an important factor to improve compliance⁴⁵.

Rouland *et al*³⁸ randomised over 400 patients to either preserved or PF latanoprost in an investigator-masked study. After 12 weeks, hyperaemia was worse in the preserved group as was the total objective ocular symptom score. However, there was no difference in the other objective signs (such as corneal staining). Furthermore, tolerance was reported as satisfactory or very satisfactory in more than 97% of patients in both groups. A survey of over 2500 patients in New Zealand⁴⁵ reported high levels of satisfaction that was associated with the frequency of drops, convenience and ease of use. The presence of side effects was not predictive of the level of satisfaction. The only side effect which was significantly greater than control group (not on medication) was hyperaemia. A recent survey by Lemij *et al* found a high treatment satisfaction rate among patients despite the presence of OSD signs,⁴⁶ though hyperaemia and ocular discomfort were the factors associated with dissatisfaction.

Preservatives in established OSD

In patients with established OSD, switching to PF medications have been shown to be beneficial to improve their symptoms, signs and tolerability. Uusitalo *et al*³⁹ in a study of those with pre-existing signs or symptoms of OSD found that symptoms after switching to tafluprost PF were reduced to one-third of baseline of latanoprost BAK preserved and signs were reduced by half. This study was limited by its open label nature and comparison of different prostaglandin analogues (rather than the same type of medication). In a randomised, double-masked, prospective study, Katz *et al*⁴⁰ found that switching to travoprost PF from preserved latanoprost in those with some OSD (mild or worse) also led to some symptom relief in those with mild OSD and in the subgroup with prior preserved drop use of more than 24 months. The corneal staining between the two groups was similar after 12 weeks. Interestingly there was more eye pain,

Table 5 Unpublished data from <https://clinicaltrials.gov> website

Comparison (ClinicalTrials.gov identifier)	Year	Duration (months)	Number of patients	Study type	Results
Travoprost (sofZia) vs Latanoprost BAK (NCT00798759)	2008	3	215	Double masked RCT	OSDI score slightly better with SofZia TBUT the same
Travoprost (sofZia) vs Latanoprost BAK (NCT00690794)	2008	3	726	Double masked RCT	OSDI change similar Absence of corneal staining similar (37 sofZia, 40 BAK)
Travoprost (sofZia) vs Latanoprost BAK (NCT00527592)	2007	Not stated	54 (comparison made between eyes)	Double masked RCT	Comfort after dose equal

BAK, benzalkonium chloride; OSDI, Ocular Surface Disease Index; RCT, randomised controlled trials; TBUT, tear breakup time.

irritation and hyperaemia in the PF group noted. Janulevičienė *et al*³⁴ measured tear film osmolarity before and after switching from BAK preserved latanoprost to tafluprost PF in patients with pre-existing OSD. They found significant improvement in tear film osmolarity as well as TBUT and corneal staining.

Batra *et al*³⁵ reported on patients with severe OSD and inadequately controlled glaucoma. They demonstrated that controlling the OSD resulted in improvement in OSD and IOP control. Measures used included lid hygiene, topical lubricants, oral doxycycline and switching to PF medications.

Skalicky *et al*⁴⁷ found that the use of more than three glaucoma medications was an independent predictor of adverse OSDI score.

Causes of variability between laboratory and clinical studies

The severity of BAK toxicity in laboratory studies and the variability in the effect found in clinical studies may partly be due to the extended duration of exposure in many of the in-vitro and in-vivo studies. In fact, clinically the concentration of BAK in the tear film diminishes very rapidly.⁴⁸

Chemical binding reduces the amount of free BAK. Additionally, the antioxidant effect of prostaglandin analogues may explain the relatively high tolerance of such medications in the longer term.¹¹ A study of conjunctival goblet cell density (CGCD)⁴⁹ found that tafluprost PF and preserved latanoprost both caused increased CGCD at 1 month. There was a sustained increase of CGCD in the tafluprost group at 6 months. This was not reversed by switching to preserved latanoprost. However, those treated with the latanoprost vehicle alone had a significant decrease. TBUT and Schirmer tests were very similar between two groups. The PF group had a lower OSDI score but were not masked to their treatment (a possible source of bias). Different prostaglandin analogues may also differ in their protective properties.⁷

There is some evidence to suggest BAK exposure may reduce corneal sensitivity and thus symptoms.⁵⁰ Furthermore, the effect of tear film osmolality in increasing BAK concentration may also explain why patients with pre-existing OSD/dry eye are more at risk.⁵¹

BAK effect on glaucoma surgical success

Trabeculectomy

A small number of studies have examined the effect of prior medical treatment on trabeculectomy success and even fewer have tried to look at the effect of BAK in particular. Broadway *et al*⁵² explored the outcome of 124 trabeculectomies. They found that a higher rate of failure was associated with long-term usage of multiple medications (all preserved, including miotics and sympathomimetics that are seldom used nowadays) and corresponding subclinical inflammatory changes in the conjunctiva. Boimer and Birt⁵³ in a retrospective study examined the results of 128 trabeculectomies. They compared BAK exposure using the number of BAK containing drops as a proxy and the dose corrected BAK exposure per day (adjusting for varying concentrations of BAK in different drops). Those with a higher number of preoperative drops and a higher dose corrected exposure had a higher risk of early trabeculectomy failure. It was not possible to calculate the cumulative dose of BAK received in each patient. However, another study of 215 trabeculectomies⁵⁴ did not find an association between the number of medications used or length of usage and trabeculectomy failure. Another study explored tear cytokines⁵⁵ demonstrated elevated levels of an inflammatory mediator (monocyte chemoattractant protein-1 (MCP-1)) in

Table 6 Cost of 1-month supply of medication in the UK

Medication	PF	Preserved	Premium, %
Bimatoprost 0.03%	£13.75	£10.30	34
Bimatoprost/Timolol	£17.94	£14.16	27
Latanoprost	£8.49	£1.43 (generic)	493
Dorzolamide/Timolol	£28.59	£1.65 (generic)	1633

PF, preservative-free.

patients taking glaucoma medications. Higher levels of MCP-1 were found with longer duration of medication use (mostly BAK preserved). Additionally, a greater risk of requiring post trabeculectomy intervention due to higher MCP-1 level was noted. However, there was no association between the number of medications and the higher risk.

PF prostaglandin analogues have been found to induce ocular adnexa macrophage infiltration, which may be partially explained by excipients in the medications.⁵⁶ Other common adverse effects of prostaglandin analogues such as orbitopathy⁵⁷ are not attributed to their preservatives. A recent Japanese study found better IOP control post-trabeculectomy in those patients who did not exhibit signs of orbitopathy due to preoperative prostaglandin analogues.⁵⁸

Broadway reported that withdrawing medications 4 weeks prior to trabeculectomy surgery and administering low potency topical steroids (fluorometholone) reduced conjunctival inflammation.⁵⁹ Breusegem reported the successful use of preoperative anti-inflammatory medications (steroids and to a lesser extent non-steroidal anti-inflammatories) to improve failure rates of trabeculectomy surgery.⁶⁰

Glaucoma aqueous shunt surgery and MIGS (minimally invasive glaucoma surgery)

No studies have examined the effects of prior glaucoma medications or preservative use on the success rate of tube surgery or MIGS procedures.

Cost issues

In general, PF preparations cost much more than the equivalent with preservative (table 6) (British National Formulary 2017).⁶¹ The premium charged by the manufacturers for the PF glaucoma medications range from 27% to over 1600%, compared with the same medications with preservatives.

From a cost effectiveness perspective, studies have linked patient satisfaction and fewer medication changes with lower costs.⁶² However, there have not been any studies directly comparing the cost effectiveness of preserved versus PF medications.

Other preservatives

While there are no clinical studies comparing non-BAK preserved drops to PF drops, there have been comparisons between non-BAK preserved and BAK preserved.

Gandolfi *et al*⁶³ randomised 371 patients to receive either BAK or polyquad preserved travoprost. At 3 months, adverse effects were generally mild and very similar in both groups.

Peace *et al*⁶⁴ compared travoprost 0.03% with polyquad to BAK preserved travoprost 0.04% and found no difference in adverse effects (a slight increase in hyperaemia in the BAK preparation group may have been related to the higher travoprost concentration). More recently Jayanthi *et al*⁶⁵ published a comparison of BAK preserved travoprost with SofZia preserved.

They reported significantly lower OSDI scores in patients on the SofZia preserved formulation. However, this study was open-labelled which may have caused some bias.

CONCLUSION/CLINICAL IMPLICATIONS

Clearly topical medications, preservatives and the excipients and buffers can cause some ocular surface changes. Laboratory and non-level one evidence demonstrate additional adverse effects from BAK. There are no data available to demonstrate that the efficacy of glaucoma medications is reduced in the absence of BAK. There is also no evidence from double-masked RCTs that BAK causes significant OSD over and above the glaucoma medication alone in patients with a healthy ocular surface.

For those on polypharmacy or with OSD, the resultant cumulatively higher dose or concentration of BAK in the tear film may mean that preservative-free preparations are desirable in patients taking more than three medications or in those with pre-existing OSD. Symptoms and signs of toxicity should be screened for those on preserved drops, as there is some evidence suggesting that switching to PF drops will improve these.

There is no conclusive evidence that BAK per se jeopardises the success rate of glaucoma filtration surgery. For those who are likely to have glaucoma filtration surgery, minimising exposure to both topical agents and preservatives may be recommended. Whether this should be in the form of earlier surgery or a preoperative washout period remains to be elucidated. This is an area in which further research is required, particularly in light of less invasive surgical options emergence.

Current evidence is inadequate due to exclusion of patients with pre-existing OSD and the short duration of many other studies. Longer-term double-masked clinical trials comparing patients on PF drops versus preserved drops would be desirable. These may not be practical due to the high cost of such studies.

As clinicians dealing with ageing populations and ever-increasing number of glaucoma patients, we should be conscious of the cost repercussions of each treatment options. Based on current evidence there is no justification for routine use of PF medication in those without significant OSD and especially those requiring only few medications (1–2) per day.

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REFERENCES

1 Rasmussen CA, Kaufman PL, Kiland JA. Benzalkonium chloride and glaucoma. *J Ocul Pharmacol Ther* 2014;30:163–9.

- 2 Freeman PD, Kahook MY. Preservatives in topical ophthalmic medications: historical and clinical perspectives. *Expert Rev Ophthalmol* 2009;4:59–64.
- 3 Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994;112:1446–54.
- 4 Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res* 2010;29:312–34.
- 5 Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: current literature and recommendations. *Curr Opin Ophthalmol* 2013;24:136–43.
- 6 Tu EY. Balancing antimicrobial efficacy and toxicity of currently available topical ophthalmic preservatives. *Saudi J Ophthalmol* 2014;28:182–7.
- 7 Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride- and polyquad-preserved combination glaucoma medications on cultured human ocular surface cells. *Adv Ther* 2011;28:501–10.
- 8 Lockington D, Macdonald EC, Stewart P, et al. Free radicals and the pH of topical glaucoma medications: a lifetime of ocular chemical injury? *Eye* 2012;26:734–41.
- 9 Pellinen P, Huhtala A, Tolonen A, et al. The cytotoxic effects of preserved and preservative-free prostaglandin analogs on human corneal and conjunctival epithelium in vitro and the distribution of benzalkonium chloride homologs in ocular surface tissues in vivo. *Curr Eye Res* 2012;37:145–54.
- 10 Liang H, Pauly A, Riancho L, et al. Toxicological evaluation of preservative-containing and preservative-free topical prostaglandin analogues on a three-dimensional-reconstituted corneal epithelium system. *Br J Ophthalmol* 2011;95:869–75.
- 11 Guenoun JM, Baudouin C, Rat P, et al. In vitro comparison of cytoprotective and antioxidative effects of latanoprost, travoprost, and bimatoprost on conjunctiva-derived epithelial cells. *Invest Ophthalmol Vis Sci* 2005;46:4594–9.
- 12 Pisella PJ, Debbasch C, Hamard P, et al. Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. *Invest Ophthalmol Vis Sci* 2004;45:1360–8.
- 13 Guenoun JM, Baudouin C, Rat P, et al. In vitro study of inflammatory potential and toxicity profile of latanoprost, travoprost, and bimatoprost in conjunctiva-derived epithelial cells. *Invest Ophthalmol Vis Sci* 2005b;46:2444–50.
- 14 Brasnu E, Brignole-Baudouin F, Riancho L, et al. In vitro effects of preservative-free tafuprost and preserved latanoprost, travoprost, and bimatoprost in a conjunctival epithelial cell line. *Curr Eye Res* 2008;33:303–12.
- 15 Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. *Arch Ophthalmol* 1994;112:1437–45.
- 16 Liesegang TJ. Conjunctival changes associated with glaucoma therapy: implications for the external disease consultant and the treatment of glaucoma. *Cornea* 1998;17:574–83.
- 17 Leal BC, Medeiros FA, Medeiros FW, et al. Conjunctival hyperemia associated with bimatoprost use: a histopathologic study. *Am J Ophthalmol* 2004;138:310–3.
- 18 Pauly A, Meloni M, Brignole-Baudouin F, et al. Multiple endpoint analysis of the 3D-reconstituted corneal epithelium after treatment with benzalkonium chloride: early detection of toxic damage. *Invest Ophthalmol Vis Sci* 2009;50:1644–52.
- 19 Khoh-Reiter S, Jessen BA. Evaluation of the cytotoxic effects of ophthalmic solutions containing benzalkonium chloride on corneal epithelium using an organotypic 3-D model. *BMC Ophthalmol* 2009;9:5.
- 20 Samples JR, Binder PS, Nayak S. The effect of epinephrine and benzalkonium chloride on cultured corneal endothelial and trabecular meshwork cells. *Exp Eye Res* 1989;49:1–12.
- 21 Kawa JE, Higginbotham EJ, Chang IL, et al. Effects of antiglaucoma medications on bovine trabecular meshwork cells in vitro. *Exp Eye Res* 1993;57:557–65.
- 22 Tripathi BJ, Tripathi RC, Millard CB. Epinephrine-induced toxicity of human trabecular cells in vitro. *Lens Eye Toxic Res* 1989;6:141–56.
- 23 Hamard P, Blondin C, Debbasch C, et al. In vitro effects of preserved and unpreserved antiglaucoma drugs on apoptotic marker expression by human trabecular cells. *Graefes Arch Clin Exp Ophthalmol* 2003;241:1037–43.
- 24 Desbenoit N, Schmitz-Afonso I, Baudouin C, et al. Localisation and quantification of benzalkonium chloride in eye tissue by TOF-SIMS imaging and liquid chromatography mass spectrometry. *Anal Bioanal Chem* 2013;405:4039–49.
- 25 Goto Y, Ibaraki N, Miyake K. Human lens epithelial cell damage and stimulation of their secretion of chemical mediators by benzalkonium chloride rather than latanoprost and timolol. *Arch Ophthalmol* 2003;121:835–9.
- 26 Herman DC, Gordon MO, Beiser JA, et al. Topical ocular hypotensive medication and lens opacification: evidence from the ocular hypertension treatment study. *Am J Ophthalmol* 2006;142:800–10.
- 27 Chandrasekaran S, Cumming RG, Rochtchina E, et al. Associations between elevated intraocular pressure and glaucoma, use of glaucoma medications, and 5-year incident cataract: the Blue Mountains Eye Study. *Ophthalmology* 2006;113:417–24.
- 28 Miyake K, Ibaraki N, Goto Y, et al. ESCRS Binkhorst lecture 2002: Pseudophakic preservative maculopathy. *J Cataract Refract Surg* 2003;29:1800–10.
- 29 Ye J, Wu H, Zhang H, et al. Role of benzalkonium chloride in DNA strand breaks in human corneal epithelial cells. *Graefes Arch Clin Exp Ophthalmol* 2011;249:1681–7.
- 30 Pisella PJ, Fillacier K, Elena PP, et al. Comparison of the effects of preserved and unpreserved formulations of timolol on the ocular surface of albino rabbits. *Ophthalmic Res* 2000;32:3–8.

- 31 Herreras JM, Pastor JC, Calonge M, *et al.* Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 1992;99:1082–8.
- 32 Jaenen N, Baudouin C, Pouliguen P, *et al.* Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol* 2007;17:341–9.
- 33 Pisella PJ, Pouliguen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 2002;86:418–23.
- 34 Janulevičienė I, Derkač I, Grybauskienė L, *et al.* Effects of preservative-free tafluprost on tear film osmolarity, tolerability, and intraocular pressure in previously treated patients with open-angle glaucoma. *Clin Ophthalmol* 2012;6:103–9.
- 35 Batra R, Taylor R, Mohamed S. Ocular surface disease exacerbated glaucoma: optimizing the ocular surface improves intraocular pressure control. *J Glaucoma* 2014;23:56–60.
- 36 Schiffman RM, Christianson MD, Jacobsen G, *et al.* Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 2000;118:615–21.
- 37 Trocme S, Hwang LJ, Bean GW, *et al.* The role of benzalkonium chloride in the occurrence of punctate keratitis: a meta-analysis of randomized, controlled clinical trials. *Ann Pharmacother* 2010;44:1914–21.
- 38 Rouland JF, Traverso CE, Stalmans I, *et al.* Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol* 2013;97:196–200.
- 39 Uusitalo H, Egorov E, Kaarniranta K, *et al.* Benefits of switching from latanoprost to preservative-free tafluprost eye drops: a meta-analysis of two Phase IIIb clinical trials. *Clin Ophthalmol* 2016;10:445–54.
- 40 Katz G, Springs CL, Craven ER, *et al.* Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost. *Clin Ophthalmol* 2010;4:1253–61.
- 41 Shedden A, Adamsons IA, Getson AJ, *et al.* Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated intraocular pressure in a randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2010;248:1757–64.
- 42 Day DG, Walters TR, Schwartz GF, *et al.* Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. *Br J Ophthalmol* 2013;97:989–93.
- 43 Goldberg I, Gil Pina R, Lanzagorta-Aresti A, *et al.* Bimatoprost 0.03%/timolol 0.5% preservative-free ophthalmic solution versus bimatoprost 0.03%/timolol 0.5% ophthalmic solution (Ganfort) for glaucoma or ocular hypertension: a 12-week randomised controlled trial. *Br J Ophthalmol* 2014;98:926–31.
- 44 Hopes M, Broadway D, Department of Ophthalmology, Norfolk and Norwich University Hospital. Preservative-free treatment in glaucoma is a sensible and realistic aim for the future. *European Ophthalmic Review* 2010;04:23–8.
- 45 Kerr NM, Patel HY, Chew SS, *et al.* Patient satisfaction with topical ocular hypotensives. *Clin Exp Ophthalmol* 2013;41:27–35.
- 46 Lemij HG, Hoevenaars JG, van der Windt C, *et al.* Patient satisfaction with glaucoma therapy: reality or myth? *Clin Ophthalmol* 2015;9:785–93.
- 47 Skaliky SE, Goldberg I, McCluskey P. Ocular surface disease and quality of life in patients with glaucoma. *Am J Ophthalmol* 2012;153:1–9.
- 48 Friedlaender MH, Breshears D, Amoozgar B, *et al.* The dilution of benzalkonium chloride (BAK) in the tear film. *Adv Ther* 2006;23:835–41.
- 49 Mastropasqua L, Agnifili L, Fasanella V, *et al.* Conjunctival goblet cells density and preservative-free tafluprost therapy for glaucoma: an *in vivo* confocal microscopy and impression cytology study. *Acta Ophthalmol* 2013;91:e397–e405.
- 50 Sarkar J, Chaudhary S, Namavari A, *et al.* Corneal neurotoxicity due to topical benzalkonium chloride. *Invest Ophthalmol Vis Sci* 2012;53:1792–802.
- 51 Clouzeau C, Godefroy D, Riancho L, *et al.* Hyperosmolarity potentiates toxic effects of benzalkonium chloride on conjunctival epithelial cells in vitro. *Mol Vis* 2012;18:851–63.
- 52 Broadway DC, Grierson I, Stürmer J, *et al.* Reversal of topical antiglaucoma medication effects on the conjunctiva. *Ophthalmol* 1996;114:262–7.
- 53 Boimer C, Birt CM. Preservative exposure and surgical outcomes in glaucoma patients: The PESO study. *J Glaucoma* 2013;22:730–5.
- 54 Öztürker ZK, Öztürker C, Bayraktar S, *et al.* Does the use of preoperative antiglaucoma medications influence trabeculectomy success? *J Ocul Pharmacol Ther* 2014;30:554–8.
- 55 Chong RS, Jiang YZ, Boey PY, *et al.* Tear cytokine profile in medicated glaucoma patients: effect of monocyte chemoattractant protein 1 on early posttrabeculectomy outcome. *Ophthalmology* 2010;117:2353–8.
- 56 Trzeziecka A, Paterno JJ, Toropainen E, *et al.* Long-term topical application of preservative-free prostaglandin analogues evokes macrophage infiltration in the ocular adnexa. *Eur J Pharmacol* 2016;788:12–20.
- 57 Kucukcivcioglu M, Bayer A, Uysal Y, *et al.* Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. *Clin Exp Ophthalmol* 2014;42:126–31.
- 58 Miki T, Naito T, Fujiwara M, *et al.* Effects of pre-surgical administration of prostaglandin analogs on the outcome of trabeculectomy. *PLoS One* 2017;12:e0181550.
- 59 Broadway DC, Grierson I, O'Brien C, *et al.* Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994;112:1446–54.
- 60 Breusegem C, Spielberg L, Van Ginderdeuren R, *et al.* Preoperative nonsteroidal anti-inflammatory drug or steroid and outcomes after trabeculectomy: a randomized controlled trial. *Ophthalmology* 2010;117:1324–30.
- 61 *British National Formulary (BNF)*. 72 edn: BMJ Publishing Group.
- 62 Denis P, University Professor, Hospital Consultant and Head, Ophthalmology Department, Croix-Rousse Hospital, Lyon, Professor U, U Consultant and Head, U, Croix-Rousse Hospital, U and . . Adverse effects, adherence and cost-benefits in glaucoma treatment. *Euro Ophthalmol Rev* 2011;05:116–22.
- 63 Gandolfi S, Paredes T, Goldberg I, *et al.* Comparison of a travoprost BAK-free formulation preserved with polyquaternium-1 with BAK-preserved travoprost in ocular hypertension or open-angle glaucoma. *Eur J Ophthalmol* 2012;22:34–44.
- 64 Peace JH, Ahlberg P, Wagner M, *et al.* Polyquaternium-1-preserved travoprost 0.003% or benzalkonium chloride-preserved travoprost 0.004% for glaucoma and ocular hypertension. *Am J Ophthalmol* 2015;160:266–74.
- 65 Jayanthi CR, Divyashree RN, Sujatha BL. Efficacy and safety of topical BAK-free travoprost 0.004% versus BAK-preserved travoprost 0.004% in the treatment of primary open angle glaucoma: a comparative study at a tertiary care hospital. *Int J Basic Clin Pharmacol* 2017;6:2199–205.