Can We Optimise the Medical Therapy of Glaucoma?

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Abstract

The use of glaucoma medications containing the preservative benzalkonium chloride (BAK) is associated with a number of ocular symptoms including ocular surface disease and dry eye syndrome. These are debilitating conditions and current strategies of therapeutic escalation compound the problem. The effects are greater in sensitive patients and rises as the number of eye drops used increases. Preservative-free antiglaucoma medications are available and should be considered in patients with primary dry eye syndrome, ocular allergy, meibomian gland dysfunction, contact lens wearing, corneal and conjunctival adverse reactions to antiglaucoma medication and pre-operative to trabeculectomy. The importance of elevated diurnal variations in intraocular pressure (IOP) in glaucoma patients was also considered.

Keywords

Benzalkonium chloride, glaucoma, intraocular pressure, tafluprost

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Managing Treatment Side-effects of Glaucoma Medications

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Current observational studies have found that all ocular symptoms and signs of irritation associated with glaucoma medications are more prevalent with preserved eye drops than with preservative-free drops.[1–6]

The prevalence of ocular surface disease (OSD) in glaucoma is high – in a study of 101 patients with glaucoma or ocular hypertension, 59 % of patients reported symptoms in at least one eye. Severe symptoms were reported by 27 % of patients. Schirmer testing showed 62 (61 %) patients with decrease in tear production in at least one eye. Severe tear deficiency was presented in 35 (35 %) patients.[4] An association was found between OSD as manifested by dry eye syndrome or corneal and conjunctival changes and the use of benzalkonium chloride (BAK)-containing medications. Each additional BAK-containing eye drop was associated with an approximately two-times higher odds of abnormal results on the lissamine green staining test.[4]

A study of 516 patients found that the severity of OSD worsened with increasing numbers of medications employed. Almost half (40 %) of the study population changed their treatment at least once owing to ocular surface concerns.[7] The study classified patients taking long-term glaucoma medication into three groups (A, B and C) according to their score on an OSD severity questionnaire. Almost half of the sample population (49 %) were in group A, 30 % in group B and 21 % in group C. Factors that correlated with the severity of OSD included patient age, number of daily eye drops, past topical treatment changes for ocular intolerance, intraocular pressure (found to be significantly higher in patients with more severe OSD) and glaucoma severity. Topical glaucoma treatment side effects were associated with a poor vision-related quality of life score.[8]

The typical strategy for managing OSD is an escalation strategy of adding preserved medications to cope with the initial problem caused by the preservative which may unfortunately initiate a vicious circle of intolerance. A clinical case was presented of dangerous escalation. The patient was taking three medications, which achieved poor intraocular pressure (IOP) control and progressive intolerance. As a result, anti-allergic eye drops were prescribed, followed by a fourth medication. The patient was then given dexamethasone/neomycin and finally Diamox™. As a result of this treatment escalation, the patient was taking nine BAK-containing eye

Table 1: Patients Who May Benefit From Preservative-free Drugs

General Condition	Frequency		
	Common	Somewhat Common	Uncommon
Dry eye independent of glaucoma	Ocular surface disease – moderate to severe dry eye symptoms (e.g. keratoconjunctivitis sicca) Ocular surface disease – moderate-to-severe blepharitis Allergic conjunctivitis Patients with Rosacea	Sjogren's contact lenses Pterygium/pseudopterygium	Patients who have undergone keratoplasty/corneal transplant Immunological conditions Stevens–Johnson Syndrome Chemical burns Ocular surface tumours Radiation injury, Aniridia Ocular cicatricial pemphigoid Keratitis associated with multiple endocrinal deficiencies Neurotrophic keratopathy Severe trachoma
Dry eye caused by glaucoma treatment	Two or more topical medications	Allergic reactions to preservatives Patients needing >20 years topical treatment for glaucoma Patients at risk for glaucoma surgery (e.g. taking 3–4 drugs but intraocular pressure still not controlled)	

Source: Leung et al., 2008.[4]

drops and had a very poor ocular surface, with an IOP of 35 mmHg. The patient was referred for surgery. Following the use of preservative-free drugs, removal of the steroid, anti-allergic eye drops and treatment of OSD, the patient's IOP dropped to 18 mmHg.

Subclinical inflammation is also a risk factor for surgical failure. Long-term use of BAK-containing glaucoma agents may result in a form of conjunctival scarring known as toxic pseudopemphigoid, in which chronic allergic reaction leads to a marked and self-sustaining inflammatory process.

It is better to consider an alternative to BAK rather than addition of medication. A number of patients may benefit from preservative-free drugs (see *Table 1*). Possible alternatives to BAK include fixed combinations and once-a-day administered eye drops which decrease the amount of BAK by 50 %. Several systems have been developed that eliminate the need for BAK – these include single dose units and preservative-free multidose bottles. Alternative techniques include selective laser trabeculoplasty (SLT). The conditions that may benefit from the use of preservative-free drops are summarised in *Table 1*.

Summary of key messages:

- The prevalence of ocular surface disease is high in glaucoma patients.
- The potential consequences of subclinical inflammation are still underestimated. They are increased in sensitive patients and with multiple treatments containing preservatives.
- 40 % of glaucoma patients changed their treatment at least once due to ocular surface concerns in a recent study.

When to Use Preservative-free Formulations – Case Studies

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The aim of this presentation was to use the results gained from clinical studies to guide ophthalmological management in six case presentations.

Case 1 was a male, aged 45 years, wearing soft contact lenses, with newly diagnosed primary open-angle glaucoma (POAG) reporting foreign body sensation. It was decided that this patient needed preservative-free antiglaucoma medication based on extensive clinical study experience of the prevalence of dry eye syndrome and OSD in POAG. Previous results supporting this decision showing that the basal tear turnover rate is reduced by 22 % in non-treated patients with POAG compared with healthy controls.[9] In a large German study of 20,506 patients with POAG, pseudoexfoliation glaucoma and pigment dispersion glaucoma, 52 % had dry eye syndrome.[3] In another study of patients (n=101) with POAG or ocular hypertension (OHT), 59 % reported dry eye symptoms in at least one eye.[4] A study (n=448) of patients with POAG or OHT found an overall OSD prevalence rate of 59.2 %, with 25.7 %, 13.2 % and 20.3 % of the patients reporting mild, moderate, or severe OSD symptoms, respectively.[10] It is also recommended that the wearing of contact lenses is avoided in dry eye syndrome.[11,12]

Case 2 was a female aged 35 years, with POAG for four years treated with dorzolamide twice a day and had bronchial asthma as well as hay fever. Allergic reactions are a hypersensitivity disorder of the immune system and occur when a person's immune system reacts to

normally harmless substances in the environment. These reactions are acquired, predictable and rapid. BAK can accumulate in ocular tissue and remain there for extended periods of time, thus prolonging adverse reactions in the cornea. It is, therefore, recommended that in cases with known allergies, BAK-containing medication is not employed as a first step. Laser treatment or surgery should be performed if the condition persists.

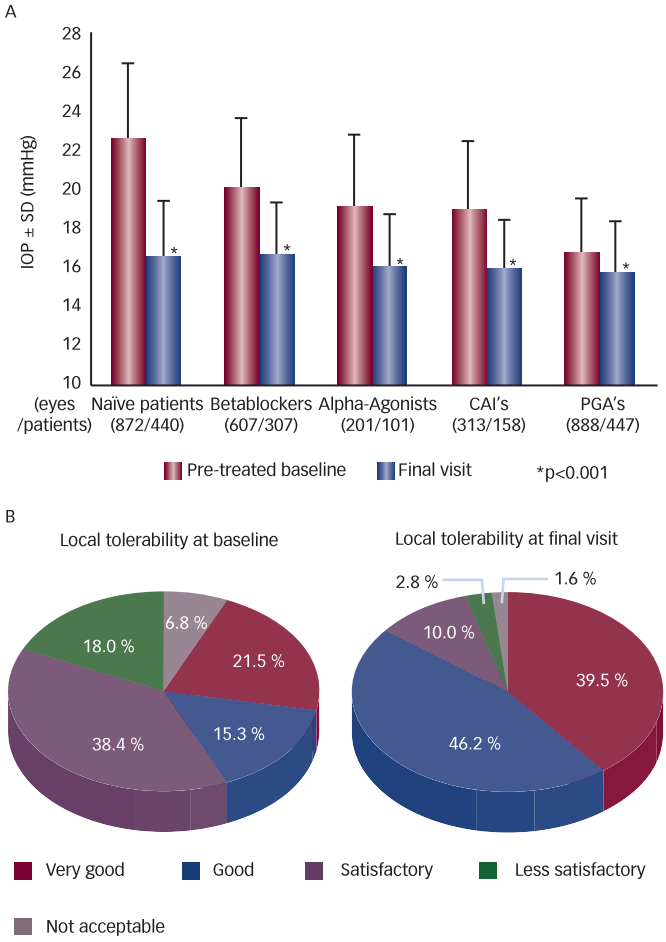
Case 3 was a male aged 67 years with pseudoexfoliation glaucoma, taking timolol and brimonidine twice a day and with dry eye syndrome as well as superficial punctate keratitis. Dry eye syndrome is common in pseudoexfoliation glaucoma with a reported prevalence of 60.9 %.[3] Pseudoexfoliative glaucoma can result in conjunctival surface changes[13] and subconjunctival crystalline calcium deposits.[14] Symptoms that are significantly increased in glaucoma patients with dry eye include foreign body sensation, red eye, pruritus, photosensitivity, blurred vision and pain. All can lead to reduced compliance. It is, therefore, recommended that this patient is given preservative-free medication.

Case 4 was a female aged 74 years with POAG, treated with timolol and dorzolamide twice a day. The patient had meibomian gland dysfunction (MGD). This is a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative and quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation and OSD, and can be caused by beta-blockers.[15] Long-term use of antiglaucoma eye drops have been associated with alterations in meibomian gland morphology and function.[16] Professor Erb has observed MGD in about 60 % of patients with POAG associated with the use of local beta-blockers and BAK.

Case 5 was a male aged 77 years with POAG, treated with bimatoprost and timolol once a day, and brimonidine twice a day. The number of eye drops containing preservatives taken per day was a cause for concern for this patient. The prevalence of signs and symptoms of ocular toxicity has been shown to be dose-dependent, increasing with the number of preserved eye drops.[1] In addition, the severity of OSD symptoms is positively correlated to the number of IOP-lowering medications used,[5] and each additional BAK-containing eye drop has been associated with an approximately two-fold higher odds ratio of showing abnormal results on staining tests.[4] The half-life of BAK in the cornea is 20 hours and, therefore, it accumulates in the cornea.[17] Furthermore, prolonged exposure to BAK causes indirect and direct toxic effects to the ocular surface, involving immunoinflammatory reactions with the release of pro-inflammatory cytokines, apoptosis and oxidative stress.[6]

Case 6 was a female, aged 77 years with normal tension glaucoma treated with brinzolamide twice a day and travoprost once a day, and illustrates the risks associated with long-term therapy with BAK-containing medications. Topical antiglaucoma medications lead to conjunctival inflammation with production of macrophages, lymphocytes and mast cells, and an increase in connective tissue and conjunctival metaplasia.[18–22] The inflammatory tear protein profile in eyes treated with long-term glaucoma medications is different from that found in primary dry eye; the tear levels of S100-A8, S100-A9, mammaglobin B and 14-3-3 ζ/δ levels have shown significant increases in groups receiving medication compared with levels in patients who were not medicated ($p<0.05$).[23] Furthermore, preservatives have been shown to thicken subepithelial collagen.[24] Preserved antiglaucoma medications are also a risk factor for failure in filtration glaucoma surgery.[25–28]

Figure 1: Results of a Prospective, Observational Study with Preservative-free Tafluprost: (A) Intraocular Pressure at Baseline and Final Visit Stratified by Previous Treatments Received, (B) Extent of Patient Satisfaction at Baseline and at the Final Visit After Tafluprost Treatment



CAIs = carbonic anhydrase inhibitors; IOP = intraocular pressure; PGAs = prostaglandin analogues; SD = standard deviation.
Source: slides 47 and 48, Erb et al., 2011.[29]

These cases clearly illustrate the need for a preservative-free glaucoma medication. This finding is supported by a prospective, multicenter, open-label observational study (n=2,123) that demonstrated preservative-free tafluprost 0.0015 % was effective, generally well-tolerated and safe in the treatment of glaucoma with ocular hypertension. In all patients, preservative-free tafluprost lowered IOP from 19.5 ± 4.4 mmHg (baseline) to 16.4 ± 2.9 mmHg after 6–12 weeks. At the start of the study, the local comfort was rated 'very good' or 'good' by 30 % of patients, but this increased to approximately 86 % at the end of the study (*Figure 1*).[29]

Summary of key messages:

- Patients with POAG have primarily a reduced basal tear turnover rate. Dry eye reduces compliance and could have a negative influence on the use of antiglaucoma eye drops.
- Preservative-free antiglaucoma medication should be considered in patients with primary dry eye syndrome, contact lens wearing with OSD, ocular allergy, meibomian gland dysfunction, corneal and conjunctival adverse reactions to antiglaucoma medication and pre-operative to trabeculectomy.

Diurnal Intraocular Pressure Variations and Medical Treatment Options

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When measuring IOP, it is important to consider fluctuations over a 24-hour period, particularly during the overnight hours that are not normally measured by ophthalmologists. Recent research underscores the importance of 24-hour IOP control to minimise pressure fluctuations. The diurnal variation of IOP in POAG is well-known and in healthy subjects typically varies by 3.17–6.5 mm Hg.[30,31] The higher the IOP the more variation.[32]

In a prospective study, patients with POAG and healthy controls showed substantial diurnal variation. During diurnal IOP measurements in an upright position there were no statistically significant differences in IOP changes between groups. However, in a supine position IOP was significantly higher than in a sitting position and increased to a greater extent in the glaucoma patients than in healthy controls.[33] Diurnal variation can be due to ageing or glaucoma, but compared with healthy eyes, the diurnal IOP is higher, the diurnal-to-nocturnal change of habitual IOP is less and the posture-independent IOP pattern around normal awakening time is different in eyes with early glaucomatous changes.[34,35] Furthermore, diurnal IOP variation changes according to glaucoma progression.[36] In patients with glaucoma and IOP in the normal range, large fluctuations in diurnal IOP are a significant risk factor. Fluctuations in IOP may be important in managing patients with glaucoma and development of methods to control such fluctuations may be warranted.[37]

The evidence regarding the impact of diurnal and long-term fluctuation is mixed. Some studies suggest that fluctuation of IOP is not a significant predictive factor of glaucoma progression.[38,39] However, most studies conclude that IOP variability seems to be an important predictor for glaucoma progression. A chart review in the US showed that when there was a 1 mmHg increase in standard deviation of IOP, glaucoma progression was 4.2 times more likely.[40] In addition, variations in this parameter are a higher risk with low IOP.

The clinical value of one-day diurnal IOP testing has not been fully validated. A recent study (n=47) found that treated POAG patients do not manifest a repeatable diurnal IOP pattern from day-to-day when measured by Goldmann tonometry.[41] However, another study (n=88) in patients with ocular hypertension or POAG found that IOP does follow a repeatable diurnal pattern.[42] One reason for this disparity in the data may be a failure to measure IOP correctly; it is very important to use the correct instrument. A study found that central corneal thickness significantly affects IOP readings obtained by applanation tonometry according to the Goldmann principle.[43] Different tonometers include the Perkins Handheld instrument, Tono-Pen handheld instrument and ocular blood flow (OBF) handheld probe pneumotonometer. Among these, the Perkins handheld instrument was found to be the most reliable of the three instruments.

Various drugs can be used to treat IOP variation, The alpha agonist 0.1 % brimonidine monotherapy has been shown to significantly lower IOP during the diurnal/wake period, however, it did not significantly lower IOP during the nocturnal/sleep period.[44] Prostaglandins reduce IOP variation throughout the day, and latanoprost, bimatoprost and travoprost have comparable efficacy.[45] However, beta-blockers do not affect IOP variation. Although both once-daily timolol and latanoprost were effective in lowering IOP during the diurnal period, only latanoprost reduced IOP during the nocturnal period.[46]

In a crossover study, preservative-free tafluprost achieved a statistically similar 24-hour IOP reduction when compared with latanoprost. Tafluprost appeared to be somewhat more effective during the night and 24-hour IOP fluctuation was significantly lower with Taflotan™ compared with latanoprost (p=0.008). Moreover, there were fewer adverse effects (AEs) with tafluprost. In patients already receiving latanoprost monotherapy, adding the carbonic anhydrase inhibitor (CAI) brinzolamide or timolol significantly reduced IOP during the diurnal period. However, only the brinzolamide add-on treatment had an IOP-lowering efficacy during the nocturnal period.[47] The additive effects of CAIs have renewed interest in these agents as an adjunct to prostaglandin therapy. Other treatments for diurnal IOP variation include pilocarpine which can effectively eliminate night peaks.

Selective laser trabeculoplasty (SLT) may be a useful treatment option for variations in IOP. In medically treated POAG patients, SLT reduced IOP more consistently during the nocturnal period than during the diurnal period.[48] In a pilot study, SLT was found to lower mean IOP and inter-visit IOP variation in normal tension glaucoma patients.[49]

Summary of key messages:

- Diurnal variations of IOP occur in glaucoma patients and are a significant risk factor in some cases.
- Alpha-agonists and beta-blockers have no IOP-lowering effect at night, but prostaglandins and CAIs are effective throughout the 24-hour period. Pilocarpine effectively eliminates night peaks. SLT also reduces nocturnal IOP peaks.
- 24-hour IOP fluctuation was significantly lower with Taflotan compared with latanoprost

Conclusion

It is evident that the unmet needs still exist in glaucoma therapy. It is important to be aware of the impact of therapy on the eye and its effect on patients' quality of life. Since glaucoma is a chronic disease, medical therapy is usually a long-term prescription, often involving multiple ophthalmic medications. The use of eye drops containing preservatives has led to a high prevalence of OSD in medically treated glaucoma patients. There is, therefore, a need to lower the preservative burden by prescribing medications without these ingredients.

Ophthalmologists also need to consider the effect of diurnal variations in IOP when prescribing medications. Glaucoma patients who appear to be stable based on daytime in-clinic IOP measurements may not be fully controlled over each 24-hour period. Prostaglandins produce a flat IOP curve over 24 hours; beta-blockers and alpha-agonists may not be as effective during the nocturnal period. Optimising the medical therapy of glaucoma should allow patients to benefit from the safest, most effective approach to preserve visual function while maximising their quality of life. ■

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