Int Ophthalmol (2019) 39:105–109
https://doi.org/10.1007/s10792-017-0792-z

ORIGINAL PAPER

Switch from BAK-preserved to preservative-free latanoprost decreases anterior chamber flare in POAG patients

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Received: 3 May 2017 / Accepted: 11 December 2017 / Published online: 22 December 2017

Abstract
Purpose To validate the hypothesis that BAK induces low-grade inflammation in the anterior chamber, we designed a study to investigate whether switching from BAK-preserved to preservative-free latanoprost in patients with primary open-angle glaucoma (POAG) would reduce the flare levels.
Patients Forty-one eyes of twenty-two patients with primary open-angle glaucoma treated with BAK-preserved latanoprost for at least 6 months as monotherapy were included. Exclusion criteria included any use of topical eye drops other than latanoprost, pseudoexfoliation and pigment dispersion glaucoma, wearing of contact lenses and intraocular surgery in the past year.
Methods At the start of the study, we measured baseline flare values. We then switched all patients to preservative-free latanoprost. After 1, 2, and 3 months, a routine ophthalmological examination was performed and flare measurement repeated.
Results Thirty-three eyes were followed up throughout the entire 3-month period. One month after the switch to preservative-free latanoprost, a statistically significant mean drop in flare of − 0.96 ph/ms ($P = 0.025$) was observed. Mean flare decreased further by − 1.31 ph/ms ($P = 0.0027$) after 2 months and by − 1.25 ph/ms ($P = 0.0041$) after 3 months.
Conclusion The switch from BAK-preserved to preservative-free latanoprost induced a statistically significant reduction in mean flare value. Whereas our previous study showed an increase in flare when initiating treatment with BAK-preserved eye drops, this study shows a decrease in flare upon cessation of BAK-preserved drugs. The combined evidence from the two studies strongly suggests that in humans BAK exerts its effects not only on the ocular surface, but also at the level of the anterior chamber.

Keywords POAG · BAK · Preservative-free · Flare · Latanoprost

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Introduction

The effect on the ocular surface of benzalkonium-chloride (BAK), the most commonly used preservative in eye drops, has received a lot of attention over

the past two decades. Both animal and in vitro studies have demonstrated that BAK causes conjunctival squamous metaplasia, apoptosis, loss of goblet cells, breakdown of the corneal epithelial barrier, and subclinical inflammation of the ocular surface. In fact, chronic exposure to BAK undermines the stability of the tear film [1]. Therefore, it comes as no surprise that several epidemiological studies have demonstrated that topical glaucoma treatment is a major risk factor for the development of ocular surface disease in glaucoma patients [2–5]. The fact that signs and symptoms of ocular surface disease are significantly lower in glaucoma patients using preservative-free drops than in patients using BAK-preserved medication clearly points to the causative role BAK plays in the genesis of this side effect [6].

If the toxic influence of BAK on the outer structures of the eye seems to be well established by now, less is known about the potential effect of BAK on the deeper structures of the eye. With millions of people taking preserved glaucoma medication daily for years or decades, it would be highly relevant to know if there is also a toxic effect of BAK on the inner structures of the eye and, if present, whether it could interfere with drug efficacy in the long run. Three in vitro studies, one on cultured human corneal endothelial and trabecular meshwork cells, one on human lens cell lines, and one on human trabecular cells, demonstrated toxicity and increased apoptotic activity related to the presence of BAK [7–9]. The key question then is whether BAK is able to penetrate the human eye in vivo. Up to now, three studies addressed this issue. Myake and co-workers investigated the effect of topical timolol and BAK in pseudophakic patients in the early postoperative period and concluded that BAK might enhance the disruption of the blood–aqueous barrier and increase the incidence of cystoids macular edema [10]. More recently, another study investigated the effect of BAK on the blood–aqueous and the blood–retinal barrier in healthy pseudophakic patients. The results confirmed that a short-term exposure to BAK can cause disruption of the blood–aqueous barrier, without altering the blood–retinal barrier. The authors discuss the mechanism of BAK-induced subclinically elevated flare levels and speculate that they are the result of a low-grade inflammation caused by the presence of BAK in the anterior chamber [11].

Finally, we showed in a previous study that administration of BAK-preserved timolol and preservative-free timolol both increase flare measurements in the anterior chamber, but that the increase is significantly higher in the BAK-treated eyes than in the preservative-free-treated eyes. In that study, we considered flare to be a proxy measure for the presence of inflammation and concluded that BAK induces a low-grade inflammation in the anterior chamber analogous to what is seen in conjunctival tissue [12].

The present study was undertaken to validate the hypothesis that BAK induces low-grade inflammation in the anterior chamber. Whereas our first study was designed to detect an increase in flare upon administration of BAK, the present study was designed to investigate whether switching from BAK-preserved to preservative-free latanoprost in patients with open-angle glaucoma would result in a reduction of the flare levels.

Methods

This prospective clinical trial was approved by the Ethics Committee of the Ghent University, and it adhered to the tenets of the declaration of Helsinki. Written informed consent was obtained from each patient.

Forty-one eyes of twenty-two consecutive patients with primary open-angle glaucoma treated with BAK-preserved latanoprost for at least 6 months as monotherapy were included. Exclusion criteria included pseudoexfoliation or pigment dispersion glaucoma, any use of topical eye drops other than latanoprost, wearing of contact lenses, and intraocular surgery in the past year.

At the start of the study, we measured baseline flare values with the laser flare(-cell) meter (Kowa FM 600) 15 min after instillation of a preservative-free drop of tropicamide. Six reliable measurements were taken, and mean flare and SD were recorded. We then switched all patients to preservative-free latanoprost. After 1, 2, and 3 months, a routine ophthalmological examination was performed and flare measurements were repeated according to the same protocol.

The laser flare(-cell) meter is an objective, quantitative, noninvasive method for in vivo evaluation of anterior segment inflammation. The instrument has proven to be reliable and the measurements to be reproducible. Flare intensity is proportional to counts of aqueous proteins and is expressed as photon counts

per milliseconds (ph/ms). Normal values for the age groups 45–75 are in the range of 4.0–5.5 ph/ms. There is, however, an increase in flare with age and a decrease with pupillary dilatation [13–18]. Normal values for the age groups 45–75 are in the range of 4.0–5.5 ph/ms [13].

Statistical methods

Sample size calculation demonstrated that for detecting a 0.8 ph/ms drop in flare after 1 month (baseline 6.5 ph/ms), a total of 30 eyes were required (80% power, 5% significance level). To assess the effect of time, we fitted a linear mixed-effects model to the flare values, accounting for paired eyes within patients. In this model, patient and eye were modeled as random effects in a nested structure. Statistical analyses were undertaken using SAS statistical software (release 9.4).

Results

From the baseline flare values of the forty-one eyes enrolled, two eyes were excluded because of high baseline flare values (> 25 ph/ms) suggestive of mild active inflammation. At month 1, one eye was excluded because of obvious viral keratoconjunctivitis. At months 2 and 3, five eyes were lost to follow-up because of drop-out, and these were older patients with logistical transportation problems.

Thirty-three eyes were followed up throughout the entire 3-month period. Figure (1) displays the mean flare values for these thirty-three eyes at baseline and 1, 2, and 3 months after the switch. After 1 month, a statistically significant mean drop in flare of − 0.96 ph/ms ($P = 0.025$) was observed. Mean flare decreased further by (to) − 1.31 ph/ms ($P = 0.0027$) after 2 months and − 1.25 ph/ms ($P = 0.0041$) 3 months after the switch to preservative-free latanoprost.

The slight increase in flare (+ 0.06) at month 3 compared to month 2 was statistically not significant ($P = 0.88$) indicating a stable situation with no further decrease of the flare 2 months after the switch from BAK-preserved to preservative-free latanoprost.

Discussion

The switch from BAK-preserved to preservative-free latanoprost induced a statistically significant reduction in mean flare value. This study confirms the results from our previous work [12] and further supports our hypothesis that BAK induces low-grade inflammation in the anterior segment, since both preservative-free beta-blockers and preservative-free latanoprost generate lower flare values than the BAK-preserved drugs.

In a previous study, a randomized prospective clinical trial, 28 previously untreated patients with ocular hypertension were given BAK-preserved timolol in one eye and preservative-free timolol in the other. Baseline flare values were compared to 1-month values. Although there was an increase in flare in both eyes, the increase was significantly higher in the BAK-treated eye. We concluded that BAK

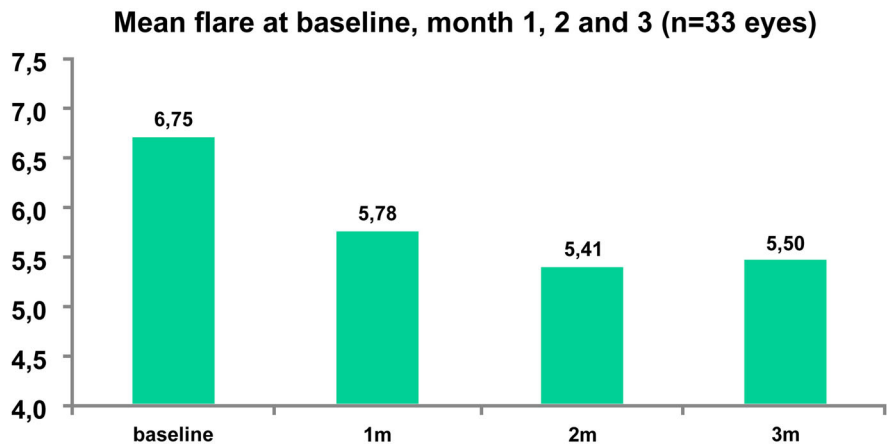

Fig. 1 Mean flare values (n = thirty-three eyes) at baseline and 1, 2, and 3 months after the switch from BAK-preserved to preservative-free latanoprost

affects not only the outer eye but also has effects on the anterior chamber.

The present study shows a decrease in flare upon cessation of BAK-preserved drugs. These findings imply two things: first, the effect of BAK on the anterior chamber does not fade over time since it is present in patients who received BAK-preserved drugs for at least 6 months; and second, even after prolonged use of BAK-preserved drugs, the effect is reversible upon cessation of BAK. The combined evidence from the two studies strongly suggests that in humans BAK exerts its effects not only on the ocular surface, but also at the level of the anterior chamber. The key question to be answered concerns the clinical relevance of this statistically significant but modest increase of flare induced by BAK. Studies have shown that BAK is highly cytotoxic for human trabecular meshwork cells in vitro [8, 9].

Knowing then that BAK-preserved glaucoma medications are often administered for years or decades and that BAK is highly cytotoxic for human trabecular meshwork cells in vitro, one might speculate that even low concentrations of BAK contribute to the high rate of apoptosis observed in human trabeculectomy specimens [19]. BAK-induced toxicity at the level of the trabecular meshwork either through apoptosis or from low-grade inflammation could provide an alternative explanation for the well-known slow loss of efficacy of glaucoma drops over time, as we discussed in detail in a previous paper.

The fact that less patients on BAK-free travoprost need adjunctive intraocular pressure lowering therapy after the first-year treatment period than patients on BAK-preserved prostaglandin analogs, as shown recently in a retrospective study from a large pharmacy claims database, is a case in point [20]. It could well be that prolonged exposure (years or even decades) to low levels of BAK in our glaucoma patients causes progressive damage of the trabecular meshwork, accounting for the well-known slow loss of efficacy of topical anti-glaucoma medication over time.

In conclusion, we demonstrated in two studies different in design that BAK may cause an increase in flare in the anterior chamber and this finding justifies further research on the potential chronic toxicity of BAK at the level of the anterior chamber structures.

References

1. Baudouin C, Labbé A, Lian H et al (2010) Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res 19:312–334
2. Jaenen N, Baudouin C, Pouliquen P et al (2007) Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol 17:341–349
3. Leung EW, Medeiros FA, Weinreb RN (2008) Prevalence of ocular surface disease in glaucoma patients. J Glaucoma 17:350–355
4. Rossi GC, Tinelli C, Pasinetti GM et al (2009) Drye eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol 19:572–579
5. Fechtner RD, Godfrey DG, Budenz D et al (2010) Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea 29:618–621
6. Pisella PJ, Pouliquen P, Baudouin C (2002) Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol 86:418–423
7. Goto Y, Ibaraki N, Miyake K et al (2003) Human lens epithelial cell damage and stimulation of their secretion of chemical mediators by benzalkonium chloride rather tha latanoprost and timolol. Arch Ophthalmol 121:835–839
8. Hamard P, Blondin C, Debbasch C, Warnet J-M, Baudouin C, Brignole F (2003) In vitro effects of preserved and unpreserved antiglaucoma drugs on apoptotic marker expression by human trabecular cells. Graefe's Arch Clin Exp Ophthalmol 241:1037–1043
9. Samples JR, Binder PS, Nayak S (1989) The effect of epinephrine and benzalkonium chloride on cultured corneal endothelial and trabecular meshwork cells. Exp Eye Res 49:1–12
10. Miyake K, Ota I, Ibaraki N et al (2001) Enhanced disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema by topical timolol and its preservative in early postoperative pseudophakia. Arch Ophthalmol 119:387–394
11. Abe RY, Zacchia RS, Santana PR, Costa VP (2014) Effects of benzalkonium chloride on the blood-aqueous and blood-retinal barriers of pseudophakic eyes. J Ocul Pharmacol Ther 30:413–418
12. Stevens AM, Kestelyn PA, De Bacquer D, Kestelyn PG (2012) Benzalkonium chloride induces anterior chamber inflammation in previously untreated patients with ocular hypertension as measured by flare meter: a randomized clinical trial. Acta Ophthalmol 90:e221–e224
13. Shah SM, Spalton DJ, Smith SE (1991) Measurement of aqueous cells and flare in normal eyes. Br J Ophthalmol 75:348–352
14. Onodera T, Gimbel HV, Debroff BM (1993) Aqueous flare and cell number in healthy eyes of Caucasians. Jpn J Ophthalmol 37:445–451
15. Guillen-Monterrubio OM, Hartikainen J, Taskinen K et al (1997) Quantitative determination of aqueous flare and cells in healthy eyes. Acta Ophthalmol Scand 75:58–62
16. Bigar F, Herbort CP, Pittet N (1991) Tyndallométrie de la chambre antérieure avec le laser Flare-Cell meter Kowa FC-1000. Klin Mbl Augenheilk 198:396–398

17. Oshika T, Kato S, Sawa M et al (1989) Aqueous flare intensity and age. Jpn J Ophthalmol 33:237–242
18. El-Harazi SM, Ruiz RS, Feldman RM et al (2002) Quantitative assessment of aqueous flare: the effect of age and pupillary dilation. Ophthalmic Surg Lasers 33:379–382
19. Baleriola B, Garcia-Feijoo J, Martinez-de-la-Casa J et al (2008) Apoptosis in the trabecular meshwork of glaucomatous patients. Mol Vis 14:1513–1516
20. Schmier JK, Coveret DW, Robin AL (2010) First-year treatment costs among new initiators of topical prostaglandin analog identified from November 2007 through April 2008. Curr Med Res Opin Published Online First: 2 November 2010. https://doi.org/10.1185/03007995.2010.531254