Are BAK-Containing Drugs Harming Our Patients?

Concerns over the preservative are not unfounded, but many questions still remain.

BY STEVEN D. VOLD, MD

Topical therapy has long been considered an optimal strategy for first-line glaucoma treatment. Among the classes of glaucoma drugs, prostaglandin analogues (or prostatics) are a popular choice because of a proven track record of efficacy, convenience (ie, once-daily dosing), and a favorable safety profile.¹⁻³

Prostaglandins, however, are antiinflammatory in nature, so they have the potential to affect the stability of the tear film and, ultimately, to harm the corneal epithelium. Additionally, many of the drugs in this class are formulated into multidose bottles requiring a preservative; benzalkonium chloride (BAK) is the most widely used agent. In in vitro and rabbit studies, BAK exposure has been associated with corneal endothelial toxicity, epithelial toxicity, and toxicity to the trabecular meshwork.⁴ A study performed in rabbit eyes published earlier this year by Brian Francis, MD, and colleagues suggested that BAK can even affect the orbicularis muscle, potentially making it difficult for the patient to close his or her eye.⁵

Although evidence of BAK toxicity is inconclusive in humans, manufacturers have released new glaucoma drugs containing lower concentrations of BAK. Meanwhile, some companies are developing drugs with proprietary preservatives to eliminate the need for BAK. When considering long-term therapy, it would make sense to use agents with lower BAK levels if they are equally efficacious. The question remains, though, whether the inclusion of BAK at any level is problematic for our glaucoma patients.

STUDY OF BAK-CONTAINING AGENTS

I participated in a study that assessed the ocular tolerability of three agents.⁶ Briefly, 164 patients with primary open-angle glaucoma or ocular hypertension were put through a 30-day run on latanoprost (Xalatan; Pfizer Inc.) monotherapy followed by a randomization to bimatoprost 0.01% (Lumigan; Allergan, Inc.) preserved with 0.02% BAK (n = 56), travoprost 0.004% (Travatan Z; Alcon Laboratories, Inc.) preserved with SofZia (n = 53), or latanoprost 0.005% preserved with 0.02% BAK (n = 55).

The investigator-masked study included patients from 16 sites in the United States and Canada. Patients were monitored for conjunctival hyperemia, corneal staining, and tear breakup time, and they were evaluated with biomicroscopy at baseline and weeks 1, 4, and 12.

There were no intergroup differences in any of the markers at any time points, save for a statistically significant difference in hyperemia at week 1 versus baseline for bimatoprost (mean hyperemia score, 0.04) versus latanoprost (mean hyperemia score, 0.00; P=.034) and travoprost (mean hyperemia score, 0.20) versus

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In the clinic, however, where patients’ adherence to topical therapy continues to be a tricky paradigm to nav-
gate, the development of any complication at any time point is a concern. Discomfort with medicine is a signifi-
cant factor affecting patients’ compliance with therapy. Therefore, it may be wise to counsel patients that they may experience some transient symptoms and to explain the importance of maintaining therapy that is intended to be long term. To borrow a commonly used phrase in other areas of eye care, if patients are told beforehand, it is an expectation, but if they find out afterward, it is a complication.

**CHANGING PARADIGM**

This study certainly has its limitations. A number of the patients had experience with treatment, with some having been on topical therapy for as long as 3 years. Additionally, given the prevalence of dry eye disease in the general population, it is likely that certain patients had baseline characteristics that could have influenced their response to the study drugs.

On the other hand, it is reassuring to have data indicating no real difference in the ocular surface tolerability of these three agents, regardless of the type of preservative. It would be hard to extrapolate out to the entire prostaglandin class or to make general claims about BAK’s tolerability, but these data give me confidence in using BAK-containing agents in the clinic.

In the real-world setting, many patients are instilling more than one drop at a time to control their glau-
coma, and certainly, there are unanswered questions about the maximal cumulative BAK load that patients can tolerate. This drug regimen would be in addition to whatever systemic medications patients may be taking, some of which may have side effects including dry eye symptomatology.

The point is that, when faced with a patient in need of treatment for glaucoma, the specialist may not be able to fully appreciate the health of the ocular surface or the individual response to a particular agent. These factors are part of my excitement about the advent of microinvasive glaucoma surgery or MIGS procedures. This new class is perfectly situated to address mild to moderate glaucoma—in some cases, at the time of cataract surgery, which can also lower intraocular pressure—without relying on patients’ remembering to take their drops.

I am also intrigued by the prospect of drug delivery devices, which could offer in essence a preservative-free multidose vial inside the eye that affects diurnal control independent of patients’ compliance. Although in the early stage of development, several injectable, contact lens-based, and intraocular drug delivery devices are in the pipeline that could be very important developments for our glaucoma patients.

**CONCLUSION**

In the future, I would like to see more studies involving BAK-containing agents where patients are rigorously screened for dry eye signs using some of the newly introduced advanced-technology diagnostics. The entire dry eye field is in a period of evolution. With several more objective measures of tear film quality emerging, researchers can gain a better understanding of the impact of popularly used topical therapies on the health of the ocular surface. It is my hope that larger-scale studies coupled with objective measures like tear film osmolarity will help close this knowledge gap. In the meantime, because of their efficacy, prostaglandins remain a viable treatment option even if the chosen agent contains BAK. Patients should be properly and thoroughly educated, however, about potential side effects.

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6.  Crichton AC, Vold S, Williams JM, Holland SKA. Ocular surface tolerability of prostaglandin analogs and prosta-