Evidence indicates the need for alternative preservatives in primary IOP-lowering therapy

According to increasing evidence, the prevalence of ocular surface disease within glaucoma patients is probably a larger issue for patients than ophthalmologists understand at this point.

The issue has received little attention in the past because there have been few first-line IOP-lowering therapies without toxic preservatives, and glaucoma sub-specialists may not focus on the ocular surface to the same extent as corneal specialists.

Primary objectives when managing glaucoma patients focus on lowering IOP over the diurnal period and preserving visual field.

Unfortunately for many glaucoma patients, the chronic therapy that is helping to preserve their vision also may be causing ocular irritation and exacerbating dry-eye symptoms over time. When these problems arise, patients become nonadherent to their medical regimen and/or may self-treat with over-the-counter (OTC) artificial tears.

Ocular surface issues are critical variables in glaucoma management. Awareness is the first step.

There is an abundance of existing evidence in clinical literature that identifies concerns about changes to the conjunctiva and the cornea related to ophthalmic preservatives or IOP-lowering medications.1 There is also good evidence that previous benzalkonium chloride (BAK) containing topical IOP-lowering therapy may negatively affect the success rates of glaucoma-filtration surgeries.2,3 Evidence also shows that the negative effects of BAK are cumulative in a long-term chronic-use scenario, such as glaucoma therapy.

An awareness of the potential for corneal complications should encourage physicians to prescribe drugs that are not toxic, especially considering the length of the treatments in glaucoma.

In addition to the clinical impact of ocular toxicity of chronic IOP-lowering therapy, there are patient-comfort considerations that also may affect patient compliance. Irritation, discomfort, and redness can encourage patients to avoid regular administration of the drugs.

Manufacturers are developing medications that are less toxic to the ocular surface, including a formulation of Travatan® without BAK.

Ocular surface conditions in glaucoma management

by Richard W. Yee, M.D.
“The real impact of this study ... is more about the fact that no damage was seen in eyes treated with BAK-free travoprost, despite the extreme dosing conditions.”

Jess T. Whitson, M.D.

**Travatan® Z solution (zero BAK) proven less toxic to the ocular surface**

by Jess T. Whitson, M.D.

**Study finds travoprost preserved without BAK does not cause epithelial toxicity**

Benalkonium chloride (BAK) is the most common preservative used in ophthalmic preparations. In high concentrations and with long-term exposure BAK can negatively affect patients’ ocular surface. This is especially concerning with glaucoma because of chronic dosing.

A recent study conducted by Walter Matthew Petroll and me at the University of Texas Southwestern Medical School evaluated a new formulation of travoprost 0.004% (Travatan® Z Ophthalmic Solution, Alcon, Fort Worth, Texas) and latanoprost 0.005% (Xalatan®) and their effects on corneal epithelial cells. The study showed that Travatan® Z does not cause corneal epithelial toxicity even under extreme dosing conditions in a rabbit model.

In contrast, the study found that commercially available Xalatan®, which is preserved with 0.02% BAK, induces superficial cell loss under similar dosing conditions. The difference presumably is linked to presence of the relatively high concentration and exposure to BAK (0.02%) in this model.

The aim of our study was to understand the effects of different medications on the corneal epithelium. In vivo confocal microscopy of New Zealand white rabbits was used to assess corneal epithelial morphology. Baseline confocal exams were performed on one eye of each animal, and two weeks later the eye was bathed with either travoprost 0.004% preserved without BAK or latanoprost 0.005% preserved with 0.02% BAK for three minutes and rinsed with balanced salt solution (BSS).

As a control, some eyes were bathed with BSS alone. The corneas were examined using in vivo confocal microscopy immediately following treatment. The corneal epithelial cells of the rabbits treated with BAK-free travoprost looked essentially normal and similar to those in the untreated eyes. The size and the morphology-visible cell borders and brightness of the nuclei-were consistent with what we see in normal eyes.

Eyes treated with latanoprost preserved with BAK displayed much smaller and more reflective surface cells. There was a significant decrease in cell area, which indicates loss of the superficial cell layer of the corneal epithelium.

These conclusions are based on the physiology of the corneal epithelium, in which the cells get larger and flatter near the surface. Because the surface cells are much larger than the cells below them, loss of those cells reveals the smaller cells below. Essentially, in eyes treated with the solution containing BAK, the superficial epithelial cells have been lost, which should be avoided clinically if possible, especially in patients with an already compromised ocular surface, such as those with dry eyes or other types of ocular surface disease.

The study’s use of extreme dosing conditions, including a three-minute bath, is not consistent with standard clinical use. However, in clinical practice, patients often are exposed to substantial amounts of BAK through multiple drops because it is a common preservative in topical glaucoma medications.

The real impact of this study is less about the finding that latanoprost 0.005% preserved with 0.02% BAK induced superficial cell loss and is more about the fact that no damage was seen in eyes treated with BAK-free travoprost, despite the extreme dosing conditions. Additional experiments are planned to identify at what concentration and dosing frequency BAK begins to cause corneal epithelial damage.

The research stems from studies we conducted using a similar toxicity model for antibiotic solutions used on the cornea, such as moxifloxacin and gatifloxacin. Those studies examined the same outcome measures of the drug’s effects on the epithelial surface. The use of IOP-lowering medications preserved with BAK is concerning due to its potential toxic effect on the corneal epithelium, especially in those patients treated with multiple topical agents.

Confocal microscopy has been used to assess corneal toxicity in several other published studies, including some that look at different detergents’ impact on an exposed cornea.
Travatan® solution provides significantly better IOP reduction

by Anastasios G.P. Konstas, M.D., Ph.D.

“... travoprost provided a statistically lower pressure later in the afternoon, at 6 p.m.”

Anastasios G.P. Konstas, M.D., Ph.D.

Travatan® patients have improved mean 24-hour IOP and maximum pressure

Physicians who treat glaucoma patients are well aware that there is increasing evidence that highlights the importance of good 24-hour pressure control to arrest glaucoma progression. However, most physicians find diurnal tests to be cumbersome, and, as a result, they are used infrequently.

In addition, more treatments have sought to minimize the IOP variation allowed in a 24-hour period, and more research is being conducted to understand how the various treatment modalities control 24-hour pressure and influence 24-hour IOP fluctuations. A recent study found that travoprost 0.004% (Travatan® Ophthalmic Solution, Alcon, Fort Worth, Texas) and latanoprost 0.005% (Xalatan®) provide patients with an effective means of reducing their IOP.

Investigators found that both travoprost and latanoprost provide significant and consistent 24-hour IOP reduction during this critical 24-hour diurnal curve from an untreated baseline but that travoprost provided a statistically lower pressure later in the afternoon, at 6 p.m. Additionally, patients showed improvements in both the mean 24-hour IOP and maximum pressure allowed.

The purpose of this non-sponsored crossover study was to evaluate for the first time the 24-hour efficacy and safety of latanoprost 0.005% compared with travoprost 0.004%, specifically in patients with exfoliative glaucoma (XFG). This is relevant because with the lack of diurnal data reflected by poor available testing, information on a drug’s diurnal fluctuations and variability would be of great use to ophthalmologists.

The study, conducted at three academic centers in Greece—a University Department of Ophthalmology, Thessaloniki, Greece, University Department of Ophthalmology, Democritus University of Thrace, Thrace, Greece, and Agio Andreas Hospital, Patras, Greece—in collaboration with the Pharmaceutical Research Network, Charleston, S.C., began with an appropriate medicine-free period of six weeks for beta blockers and prostaglandin analogues.

XFG patients with a pressure of 24 mm Hg or higher were randomized to either latanoprost or travoprost for an eight-week treatment period. Patients were then switched to the opposite treatment for the second period. At untreated baseline and at the end of each treatment period, patients underwent 24-hour IOP assessment at 6 a.m., 10 a.m., 2 p.m., 6 p.m., 10 p.m., and 2 a.m.

IOP results for 40 completed XFG patients established a greater statistical reduction of IOP by travoprost for the 24-hour curve as well as at the 6 p.m. mark. At 6 p.m., the mean pressure for travoprost was 16.7 ± 2.6 mm Hg and 17.9 ± 2.5 mm Hg for latanoprost. Both PG analogues obtained a significant reduction in 24-hour fluctuation of pressure.

References
1. Konstas AG, Vasillios KP, Ioannis KE, Nikolaos L, Stavrenia K, Stewart WC. 24-hr IOP efficacy and safety of latanoprost 0.005% versus travoprost 0.004% each given every evening in exfoliative glaucoma patients. Presented at: World Ophthalmology Congress; February 19-24, 2006; Sao Paulo, Brazil.

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prevent normal physiology and metabolism of the cells exposed to it. A substantial amount of research exists that suggests we should consider using chronic therapies with alternative preservative systems that are less toxic to the ocular surface.

References
Travatan® solution provides enduring IOP control despite missing a dose

by Arthur J. Sit, S.M., M.D.

"Should patients forget to dose, the enduring IOP-lowering efficacy of Travatan® continues after the 24-hour period."

Arthur J. Sit, S.M., M.D.

Study indicates IOP-lowering effect of Travatan® continues through the nocturnal period, when pressure spikes are common

Our recent research has found that the IOP-lowering effect after omission of one to two doses of travoprost 0.004% (Travatan® Ophthalmic Solution, Alcon, Fort Worth, Texas) is attenuated in the daytime period but sustained in the nocturnal period, the time corresponding to the highest IOP in most individuals.

Previous research at the Hamilton Glaucoma Center, University of California, San Diego, examined the 24-hour efficacy of prostaglandin analogues and indicated that they are effective throughout the 24-hour period, while other medications (timolol, in particular) had good diurnal efficacy but minimal nocturnal efficacy. Research by others suggested that the duration of efficacy of prostaglandins could be significantly longer than the standard 24-hour dosing period.1,2 No previous study examined whether there was a difference between diurnal and nocturnal periods in duration of efficacy for prostaglandin analogues.

Our study aimed to assess the diurnal and nocturnal persistency of IOP reduction after omission of up to two doses of Travatan® in patients with open-angle glaucoma or ocular hypertension. The prospective, open-label study followed 20 subjects for three sessions of 24-hour IOP monitoring. The first session occurred before initiating treatment of newly diagnosed patients or after a four-week washout among patients already receiving medical therapy. The second session occurred after four weeks or more of travoprost treatment. The third session was performed 41 to 63 hours after the last travoprost dose.

We found that travoprost maintained IOP reduction between 41 to 63 hours after the last dose, well beyond the normal 24-hour dosing period. Although a similar effect had been described first by others, we were surprised to find the diurnal IOP reduction decreased with one or two missed doses while the nocturnal IOP reduction was sustained even after two missed doses. This had not been reported previously, and it was not a result we could anticipate.

"Should patients forget to dose, the enduring IOP-lowering efficacy of Travatan® continues after the 24-hour period."

Arthur J. Sit, S.M., M.D.

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Mean IOP values lower for Travatan® recipients

Physicians seeking improved IOP control throughout the day may find benefits in Travatan® Ophthalmic Solution (travoprost 0.004%, Alcon, Fort Worth, Texas).

In a study presented at the Association for Research and Vision in Ophthalmology (ARVO) meeting of the American Glaucoma Society, 2006, travoprost 0.004%, which aims to improve non-conventional outflow in primary open-angle glaucoma, produced significantly greater IOP-lowering efficacy compared with latanoprost 0.005% (Xalatan®). The effect was measured at 5 p.m., approximately 20 hours after dosing.

The results came from a six-week, double-masked, open-label study that compared the IOP-lowering efficacy and safety of once-daily latanoprost 0.005% for six weeks and once-daily travoprost 0.004% in patients with open-angle glaucoma or ocular hypertension.

The randomized, multicenter, parallel, actively controlled study included 155 patients in the travoprost 0.004% treatment group and 147 patients in the latanoprost 0.005% group. Study participants received their medications once-daily at 9 p.m., and all IOP measurements were taken at 5 p.m. (±1h; 19 to 21 hours post-dose).

The study found mean IOP values were lower for travoprost recipients at all time points during the six-week study (P > 0.05). The differences in mean IOP change from baseline during the four on-therapy visits all favored travoprost therapy. The difference in pooled IOP reductions from baseline was highly statistically significant.

Travoprost recipients had a mean IOP reduction of 8.3 mm Hg, while latanoprost had a mean IOP reduction of 7.5 mm Hg during the masked phase of the study.

This may be an important finding, as it has been reported that up to 59% of patients fail to take their medication as prescribed. Should patients forget to dose, the enduring IOP-lowering efficacy of Travatan® continues after the 24-hour period.

The persistence of the nocturnal lowering of IOP may be particularly important, as it is during this time of day that almost two-thirds of glaucoma patients have their peak IOP. Up to 80% of patients reportedly fail to take their medication as prescribed. Should patients forget to dose, the persistent IOP-lowering of travoprost beyond the 24-hour period may be beneficial.

Other studies have examined persistent IOP reduction with prostaglandin analogues but did not examine the nocturnal versus diurnal differences. Our study was performed on patients with open-angle glaucoma or ocular hypertension requiring treatment. Caution is necessary in any attempt to extrapolate the results to different patient populations. However, at this point, we do not have any reason to suspect that the results would be inapplicable to other types of glaucoma in which prostaglandin analogues are used effectively.

References
The Travatan™ Dosing Aid accurately records when drops are dispensed from a bottle of Travatan® Ophthalmic Solution, found a recent study. The dosing aid is designed to hold a bottle of Travatan® (travoprost 0.004%, Alcon) and help patients administer the medication. Physicians can use the information from the dosing aid to target compliance efforts of patients who don’t take their medicine as prescribed.

Although the only proven treatment to prevent the progression of glaucoma is lowering IOP, few publications have reported on patients’ actual use of topical ocular hypotensives. There is now a large body of literature documenting that not all patients take their medications as prescribed, and it is estimated that, on average, less than 70% of prescribed doses are taken.

The dosing aid’s accuracy at recording when drops are administered was assessed in a recent study conducted by David S. Friedman (M.D.) at Wilmer Eye Institute, Johns Hopkins University, Baltimore. Five physicians and 20 patients used the dosing aid, and logs of usage were compared to dosing aid recordings. The data were automatically downloaded from the device. The first part of the study asked patients to use the dosing aid for one week after viewing a brief instructional video. Patients were called at home twice each day to use the dosing aid. Patients were instructed to dispense one drop into the sink in the morning—not into their eye—to accumulate more data over the week of the study.

In addition, patients administered the evening drop into their eye using the dosing aid. Both administrations were done while an observer waited for confirmation on the phone to ensure the dosing aid was used and to be certain of the time.

Among patients, 93% of drops were recorded, and more than 85% of the drops were recorded in 18 of 20 subjects. The study also assessed how patients felt about using the device. Most of them preferred using the device to using the bottle alone.

The device’s alarm and flashing drop icon are compliance reminders, but these components were not activated for this study. Data from the dosing aid can be downloaded directly onto a physician’s computer, allowing him to easily retrieve data on when and how often patients are taking their drops.

Features of the TRAVATAN™ Dosing Aid

Having these data will assist physicians in identifying noncompliant patients, hopefully allowing them to target their efforts at improving compliance. These data also will show the patterns of noncompliance and could help identify obstacles to compliance that may arise at certain times—weekends, for instance.

The device appears to trump other compliance-tracking methods such as pharmacy data, patient reports, and patient diaries, which all are well documented to be imperfect. Such tracking methods tend to overestimate compliance. A device that records attempts to take an IOP-lowering drop could help determine whether a particular intervention actually worked.

The device also would prevent, or identify, practicing strict compliance only for a few days before an appointment, which may produce apparently controlled IOP measurements in the office but could obscure erratic dosing and IOP fluctuation. Patients could benefit from continued use of the device.

Given the recent documentation of widespread under-compliance with medical therapy, the dosing aid could be a useful addition to clinical care.
**Travatan™ Dosing Aid may improve patient compliance**

by Brian E. Flowers, M.D.

**Medication-tracking device widely accepted by physicians**

A n assessment of patient and physician comfort with the Travatan™ Dosing Aid (Alcon, Fort Worth, Texas) found broad acceptance of the device.

A single-arm, open-label, 10-center study of 87 patients with open-angle glaucoma or ocular hypertension who were currently on prostaglandin analogue monotherapy and satisfied inclusion/exclusion criteria assessed their views of the device, which dispenses Travatan® Ophthalmic Solution (travoprost 0.004%, Alcon).1

The patients used the device—which reminds them when to dose their medication, aids in dispensing the drug, and records the time and date of dosing—once daily at about 9 p.m. for four weeks and then completed a questionnaire.

Patients said that the dosing lever and the visual alarm were the dosing aid’s most favored features, with 69% reporting that they would continue using it, and 92% indicating that they were not concerned that the device electronically monitors their compliance.

The dosing aid’s lever to ease drop dispensing initially wasn’t considered a major feature, but it addresses a common concern of a large subset of glaucoma patients—older patients who have trouble dispensing glaucoma medication. Interestingly, many patients said it was their favorite of the device’s features.

It also was significant and somewhat surprising that patients were not disturbed by having their behavior monitored.

The physicians involved also completed a questionnaire before the first patient was screened and after the last patient exited the study. Physicians reported that they found the dosing aid helpful in counseling patients on compliance and that they would recommend 91% of their patients to continue to use it. All participating physicians stated they would recommend the dosing aid to future patients.

Physicians said the device’s ability to record the time and date of dosing makes it a useful tool for assessing patient compliance. The device provides easy access to the data it collects through a connection with a physician’s computer, allowing physicians to track how frequently their patients use the device and how many drops were taken.

The first step in improving compliance is identifying lack of compliance, something that heretofore has been challenging. Physicians have had to guess patients’ compliance, and although physician experience may help, we are poor at determining compliance levels.

Limited previous research in this area showed mixed results. But this research is an early example of a glaucoma drug-dispensing device that patients can take home and that provides physicians with a reliable dosing record. That combination makes this device a groundbreaking achievement.

**References**

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