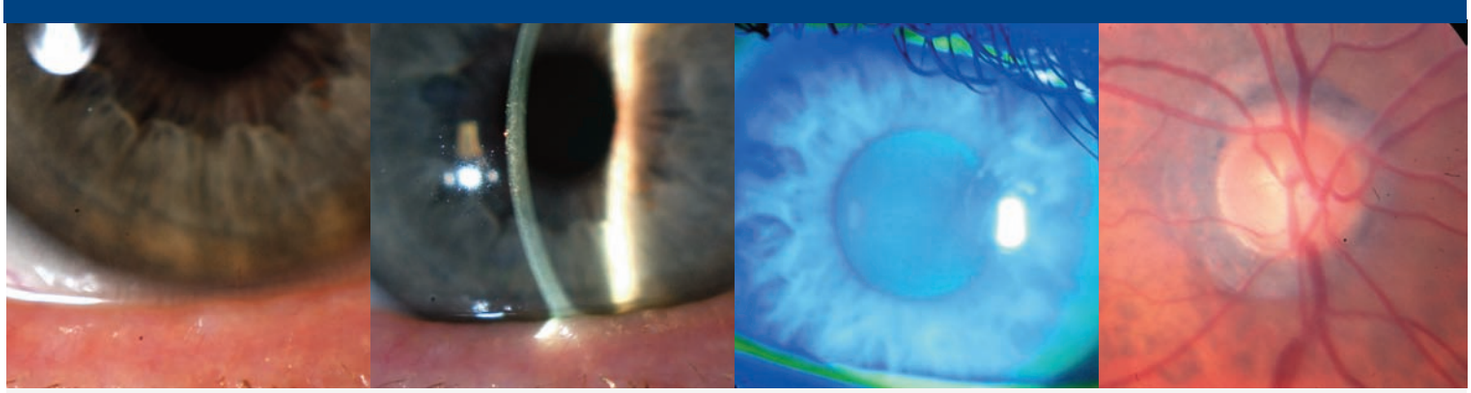
CONTINUING MEDICAL EDUCATION

A SUPPLEMENT TO
Ophthalmology MANAGEMENT
OCTOBER 2008

Managing Ocular Surface Disease In the Glaucoma Patient

Experts discuss the impact of BAK-preserved medications on the ocular surface and the role BAK-free prostaglandins play in the treatment and management of this patient population.



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COMPLETION TIME
The estimated time to complete this activity is 1 hour.

TARGET AUDIENCE
This CME is intended for all ophthalmologists.

EDUCATIONAL OBJECTIVES
Upon completion of this educational activity, participants should be able to:

1. Recognize the prevalence of ocular surface disease in glaucoma patients.

2. Understand the long-term effects of glaucoma medications on the ocular surface.

3. Discuss recent research linking an increase in ocular surface disease to IOP-lowering medications containing benzalkonium chloride (BAK).

4. Learn how to assess, treat and manage ocular surface disease while monitoring the effects of glaucoma therapy.

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METHOD OF PARTICIPATION
Read the articles and pass the post-test by Sept. 30, 2009.

Release date: September 2008
Expiration date: September 2009

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By Robert D. Fechtner, M.D.

Ocular Surface Disease in Glaucoma Patients: Prevalence and Treatment Options

Efficacy, safety and tolerability are the most important factors when prescribing topical therapy. So it's important to stay alert to subtle signs and symptoms signaling a problem with the ocular surface.

Advances in medical therapy for glaucoma have produced a wide array of options for lowering intraocular pressure (IOP), enabling us to tailor treatment to each patient's individual needs and characteristics. Despite these advances, we're still treating a chronic disease that requires long-term therapy rather than providing a cure.

Long-term therapy with all topical IOP-lowering medications is associated with the potential for adverse effects, some of which are more obvious, such as allergy, discomfort, iris and periocular skin color changes or exacerbation of pulmonary disease. Others are more subtle. Therefore, when evaluating the benefits of any glaucoma therapy, we must be aware of and periodically reassess the potential long-term burdens and consequences of treatment.

This continuing medical education activity addresses one aspect of chronic topical IOP-lowering therapy: the incidence of ocular surface disease (OSD) among treated patients with glaucoma and the impact of topical glaucoma medications on the ocular surface.[1]

Prevalence of OSD

Recent studies,[2,3] including one in which I participated, have demonstrated that OSD symptoms are much more prevalent among treated glaucoma patients than previously suspected. As our colleagues who specialize in corneal health are well aware, one of the challenges facing clinicians is that an absence of objective clinical signs of OSD, such as staining or decreased tear breakup time, doesn't reliably indicate that a patient is free of OSD symptoms. Patients without clinical signs often complain of symptoms that may indicate underlying OSD. These symptoms can negatively affect a patient's quality of life and, for glaucoma patients, their willingness to adhere to prescribed therapy, which we want to avoid.

We surveyed more than 600 patients with glaucoma using the Ocular Surface Disease Index (OSDI),[4] a validated questionnaire designed to grade disease severity in patients with subjective symptoms. In our sample, nearly 50% of patients who were using IOP-lowering eye drops experienced mild, moderate or severe symptoms of OSD, and more than 25% were graded as having moderate to severe symptoms.

Furthermore, we found a correlation between the number of IOP-lowering medications a patient used and the OSDI score. This correlation raises the following questions: Are we unwittingly overlooking dry eye symptoms in our glaucoma patients? And what impact do glaucoma drops have on the ocular surface?

Questionable Preservative

Undoubtedly, local and systemic adverse effects are well recognized and appropriately attributed to the medications patients use to lower IOP. But there are other aspects of formulations that can impact comfort and tolerability — namely, the preservatives they contain. We've long accepted that benzalkonium chloride (BAK), used in most topical IOP-lowering medications, is highly effective. But we've also recognized that it has a negative impact on ocular tissues. Research has shown that BAK can injure ocular tissues in vitro and in animal models, and evidence is emerging that it may contribute to problems with the ocular surface.[5] The availability of a prostaglandin and other topical medications with alternative preservative systems has led us to reconsider the role of BAK in ophthalmic preparations and chronic IOP-lowering treatment.

Recently, Henry and colleagues[6] used the OSDI to survey patients who, in the opinion of their treating ophthalmologist, required a change in therapy owing to tolerability problems. After completing a baseline OSDI, subjects discontinued their previous treatment with either latanoprost (Xalatan, Pfizer Inc.) or bimatoprost (Lumigan, Allergan Inc.), and were prescribed travoprost preserved with sofZia (Travatan Z, Alcon Laboratories Inc.). After using travoprost preserved with sofZia for

Glaucoma Medications With BAK

- Brinzolamide (Azopt, Alcon Laboratories Inc.)
- Betaxolol (Betoptic S, Alcon Laboratories Inc.)
- Bimatoprost (Lumigan, Allergan Inc.)
- Brimonidine tartrate/timolol maleate (Combigan, Allergan Inc.)
- Carteolol ophthalmic solution (Ocupress, Bausch & Lomb)
- Dorzolamide hydrochloride/timolol maleate (Cosopt, Merck & Co.)
- Dorzolamide hydrochloride (Trusopt, Merck & Co.)
- Latanoprost (Xalatan, Pfizer Inc.)
- Levobunolol hydrochloride (Betagan, Allergan Inc.)
- Timolol maleate (Timoptic, Merck & Co.)
- Travoprost 0.004% (Travatan, Alcon Laboratories Inc.)

Glaucoma Medications Without BAK

- Travoprost with sofZia (Travatan Z, Alcon Laboratories Inc.)

Glaucoma Medications With Purite, a Gentler Preservative

- Brimonidine tartrate (Alphagan P, Allergan Inc.)

3 months, the patients again completed the OSDI. IOPs remained controlled, and reductions in OSDI scores were statistically and clinically significant. On average, the group with severe symptom scores moved to moderate; the moderate group moved to mild; and the mild group moved to normal. The magnitude of the score reduction was greatest among patients who initially had reported the most severe symptom scores. Although this study was open label, it suggests that switching to travoprost preserved with sofZia reduced OSD symptoms in patients previously treated with other prostaglandins.

Treatment Modification Options

Because the prostaglandin analogues are so effective at controlling IOPs, they remain our most common choice as initial monotherapy in patients with glaucoma. However, we should be aware that our patients who are using IOP-lowering drugs also are using other OSD treatments concurrently. We often take an additive approach to OSD with lubricants, prescription medications and punctal plugs. We can simply look at all the treated glaucoma patients who are using tear supplements. So we shouldn't neglect other underlying conditions, such as meibomian gland disease, and environmental factors (ie, low ambient humidity, ocular medications) that can be modified to improve OSD. One factor we shouldn't overlook is BAK-preserved medications. While the use of multiple drugs can result in an additive benefit to controlling IOPs, this strategy also can increase a patient's total BAK burden. We now have options for both initial and adjunctive treatment that can reduce the BAK burden on the ocular surface.

Topical Meds, the Ocular Surface

Three different prostaglandins (bimatoprost, latanoprost and travoprost) and three additional modern classes of alternatives or adjuncts (alpha-adrenergic agonists, beta-adrenergic antagonists and topical carbonic anhydrase inhibitors) are available to lower IOPs in patients with glaucoma. In the future, we'll continue to see new formulations and alternative preservative systems. An analysis of the ingredients in any of the medications used for treating glaucoma will reveal that the therapeutic compound represents only a very small percentage of each preparation. For example, the most common beta-adrenergic antagonist solution is 0.5% timolol and 99.5% other substances.

Formulary restrictions and the need for many patients to use adjunctive therapy leave us with several IOP-lowering medications that contain BAK. But when glaucoma patients who are using BAK-preserved eye drops have symptoms or signs of OSD, we can offer alternative treatment options. For this reason, we must first be aware of not only the clinical signs of OSD, but also of the subjective symptoms that may indicate patients are in the early stages of the disease. Removal of BAK alone may not eliminate all ocular surface problems, but it can be a helpful step forward. **OM**

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By Robert D. Fechtner, M.D., and David S. Chu, M.D.

Tracking Preservatives Keeps Glaucoma and Cornea Specialists in Sync

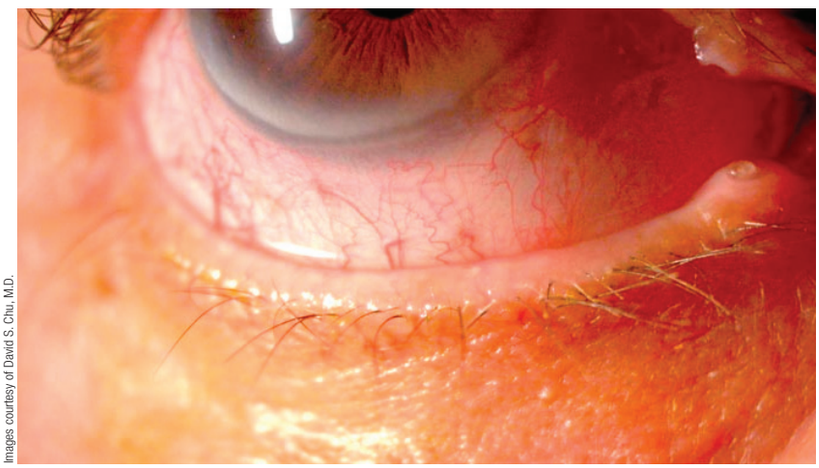
When a patient's glaucoma medications make it difficult to treat his ocular surface disease effectively, doctors from both specialties need to collaborate.

We often treat glaucoma and ocular surface disease (OSD) simultaneously over long periods of time. Both problems affect older people disproportionately. In some cases, however, shared risk factors aren't the only reasons for patients to have both glaucoma and OSD. A recent case helped raise awareness of this problem among colleagues in two specialties.

Parallel Courses of Therapy

The glaucoma service often shares patients with the cornea service. This was the situation with one 83-year-old woman, about whom I was periodically consulted for glaucoma while my cornea colleague was treating her for OSD. As we each tried to do our best in our area of specialty, we realized we shared a common problem — ocular surface disease.

The patient had relatively good visual acuity of 20/25 OU. Her intraocular pressures (IOPs) were moderately controlled (19 mm Hg OD and 20 mm Hg OS) with dorzolamide hydrochloride (Trusopt, Merck & Co. Inc.) b.i.d. and bimatoprost (Lumigan, Allergan) q.i.d. The cornea specialist was treating the patient's OSD symptoms with topical lubricants and cyclosporine (Restasis, Allergan Inc.) b.i.d. He had inserted punctal plugs to increase the tear volume on the cornea. Despite these measures, the patient still reported OSD symptoms.



Images courtesy of David S. Chu, M.D.

Figure 1. Treatment with punctal plugs, cyclosporine and artificial tears hasn't improved this patient's ocular surface disease.

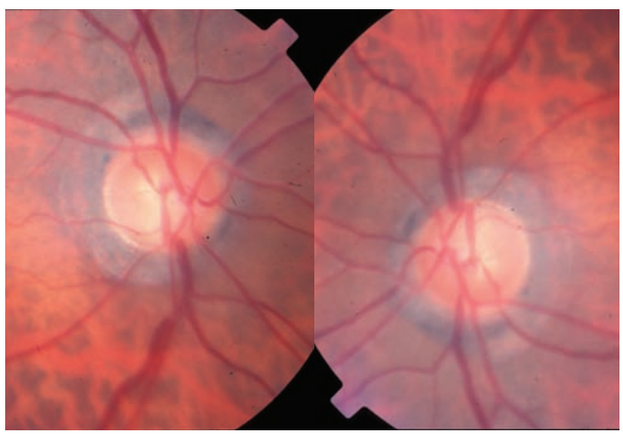


Figure 2. The optic nerve is thin to absent inferiorly in the right eye and shows marked thinning superiorly in the left eye. The thinning correlates with the patient's visual field defects.

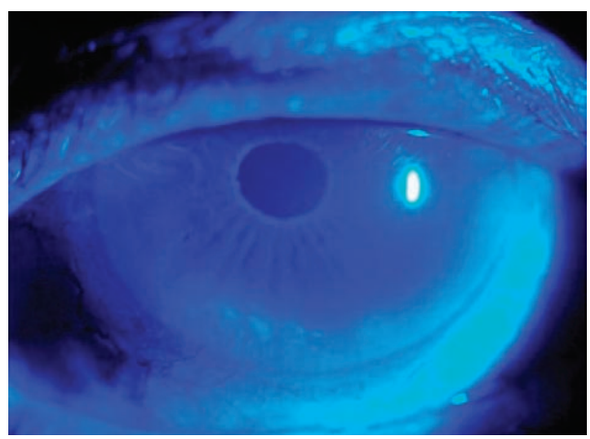


Figure 3. Fluorescein staining reveals that dry eye has badly disrupted the corneal epithelium.

Therapeutic Paths Merge

At a scheduled visit, the patient complained that she still experienced ocular discomfort and blurry vision intermittently. Upon examination, I confirmed that the punctal plugs were still in place. The patient exhibited marked meibomian gland disease (**Figure 1**).

- **Optic nerve:** Photos showed that the optic nerve rim was nearly absent inferiorly OD; and there was marked thinning superiorly OS, consistent with the visual field defects (**Figure 2**).
- **Fluorescein staining:** There was punctate staining of the corneal epithelium (**Figure 3**).
- **Visual fields:** The patient had moderately advanced visual field disturbances OD and moderate disturbances OS (**Figure 4**).

Despite the various therapies employed to resolve the OSD, the patient was still symptomatic and uncomfortable. The glaucoma regimen remained the same for several years. Recognizing that her glaucoma medications might be contributing to her ocular surface problems,[1,2] the cornea specialist and I decided to alter the glaucoma therapy.

Removing the BAK

The patient was using two glaucoma medications that contained benzalkonium chloride (BAK). We switched her to travoprost with sofZia (Travatan Z, Alcon Laboratories Inc.). This change eliminated the BAK and reduced the patient's total drop burden to 1 drop per day. We re-emphasized the need for the patient to apply hot compresses and express the meibomian secretions twice daily for meibomian gland dysfunction. As an additional measure to control IOP, while sparing the ocular surface, we prescribed a low dose of oral methazolamide (25 milligrams b.i.d.). At follow up, the patient reported that her eyes felt more comfortable and her vision had improved, although the measured acuity didn't change. The new regimen controlled the patient's IOPs at previous levels — mid-to-high teens OD and high teens OS. The ocular surface is better, although I'm not certain these levels are sufficient. Laser or incisional glaucoma surgery may be needed.

Working in Sync

This experience raised awareness in my clinic about the importance of knowing the full scope of a patient's concurrent ocular diseases and treatment regimens. Certainly, I knew the patient had ocular surface disease, but I wasn't satisfied with the IOP control and didn't fully appreciate the impact of the topical treatment on the ocular surface. Now, every glaucoma patient who's using artificial tears gets additional attention to determine the possible underlying factors contributing to OSD.

Many glaucoma patients have symptomatic OSD. Part of their treatment for OSD is to consider the possible contribution of topical IOP-lowering medications and change the glaucoma treatment accordingly.[1,2] The availability of BAK-free glaucoma treatments enables us to eliminate at least one irritant for patients with glaucoma and OSD. **OM**

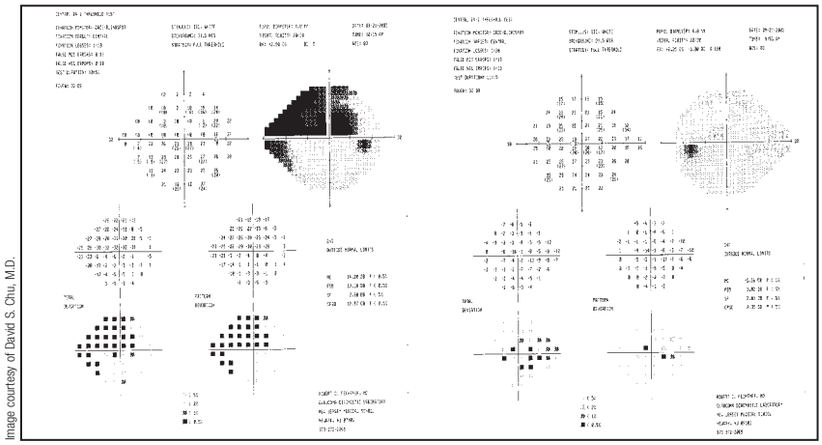


Image courtesy of David S. Chu, M.D.

Figure 4. Visual field testing shows moderate to advanced disturbances in the right eye and moderate disturbance in the left eye.

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OSD Signs and Symptoms Improve After Eliminating BAK-preserved Medications

Presentation and Chief Complaint

A 58-year-old woman presented with a 9-year history of open-angle glaucoma in both eyes. Her target IOP in the past had been 16 mm Hg OU, and although her pressures usually were in the target range, she complained of frequent foreign body sensation and discomfort in both eyes (**Figure 1**).

At the time of this initial visit, the patient's ocular medications included latanoprost (Xalatan, Pfizer Inc.), 1 drop in each eye daily and preserved artificial tears p.r.n. She'd previously been using brimonidine tartrate/timolol maleate (Combigan, Allergan Inc.), but I had discontinued both because she couldn't tolerate them.

Examination

The patient's best-corrected visual acuity (BCVA) was 20/25 OU. Her IOPs were 17 mm Hg in the right eye and 15 mm Hg in the left eye. Her cup-to-disc ratio was 0.7 in the right eye and 0.6 in the left eye. Humphrey visual field testing revealed early nasal steps in both eyes. Ocular surface assessment showed significant punctate epithelial changes on both corneas. Tear breakup time (TBUT) was 3 seconds in each eye (**Figure 2**).

Treatment Plan

Because of the patient's history of significant ocular discomfort, we discontinued latanoprost and prescribed another prostaglandin analogue, travoprost preserved with sofZia (Travatan Z, Alcon Laboratories Inc.), which doesn't contain the preservative benzalkonium chloride (BAK). In both animal and human studies, BAK has been shown to have negative effects on ocular surface health, especially with chronic application. (See "Impact of BAK-free Prostaglandins in the Management of Ocular Surface Disease" on page 8.) We also recommended that the patient switch to preservative-free artificial tears.

Results

When the patient returned for follow-up 4 weeks later, her BCVA was 20/25 in both eyes. The punctate epithelial changes observed at the initial visit were improved, and the patient reported significant improvement in her ocular comfort. She was using the preservative-free tears once every several days. Her IOPs were 15 mm Hg in both eyes, and her TBUT had increased to 7 seconds in both eyes. We recommended that the patient continue with the prescribed treatment, and no further changes in treatment have been required.

—Richard S. Davidson, M.D.

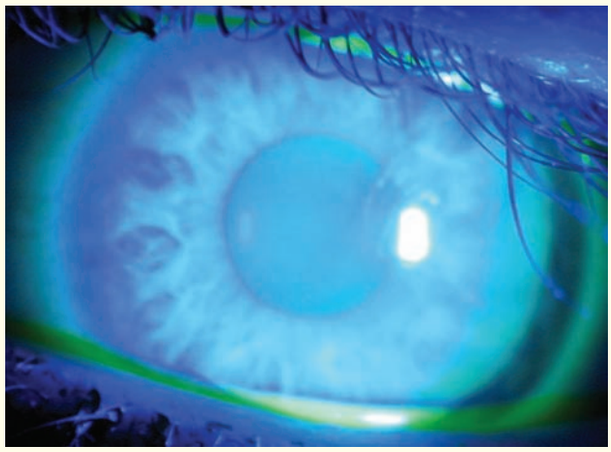

Figure 1. Fluorescein dye covers the corneal surface in this patient, who presented with complaints of frequent foreign body sensation and discomfort OU.

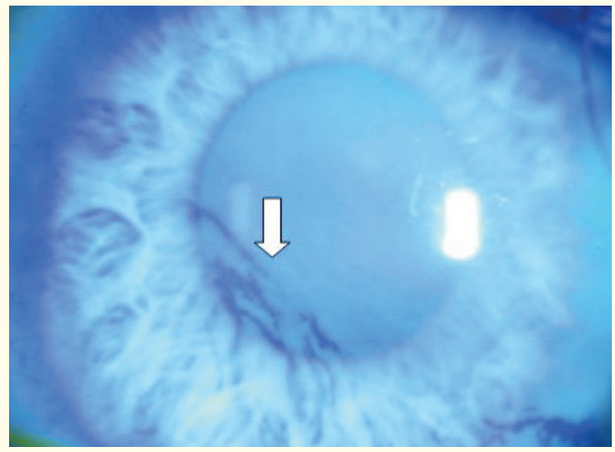

Figure 2. The white arrow indicates tear film breakdown at the patient's initial visit, before switching to BAK-free medications.

Impact of BAK-free Prostaglandins in the Management of Ocular Surface Disease

Data from preclinical and clinical studies are raising clinicians' awareness of ocular surface disease in glaucoma patients. Learn how you can help your patients who are susceptible to this condition.

While approximately 11% of the population can be expected to exhibit signs and symptoms of ocular surface disease (OSD), the condition appears to be more prevalent among patients with glaucoma.[1,2] The recent study[2] by Leung and colleagues, using the Ocular Surface Disease Index (OSDI) for measuring dry eye symptoms, showed that 59% of patients reported OSD symptoms in at least one eye. In a recent multicenter trial[3] involving 630 patients being treated for glaucoma, 48.4% were found to have an OSDI score of mild, moderate or severe.

Several factors likely contribute to a higher rate of OSD among glaucoma patients. As a group, they're older than the general population, making them more likely to have decreased tear production. They're also more likely to be taking systemic medications for a variety of conditions, such as hypertension, allergy or depression, which have cholinergic properties and, therefore, ocular drying effects.[4]

An often overlooked contributor to OSD in the glaucoma population is benzalkonium chloride (BAK), a detergent-type preservative present in 72% of the ophthalmic medications in use today. The FDA requires all ophthalmic preparations to meet the United States Pharmacopeia standards for antimicrobial effectiveness. In addition to this protective effect, BAK also prevents biodegradation of the medications and, in some cases, enhances corneal penetration by causing epithelial separation. In glaucoma medications, the concentration of BAK ranges from 0.005% to 0.02%.

Effects of BAK: Preclinical Studies

A large body of evidence derived from preclinical studies has elucidated the effects of BAK-preserved glaucoma medications on the ocular surface.[5–7] When comparing medications with and without BAK, researchers found that formulations containing BAK have significant cytotoxic effects on human conjunctiva-derived cells. These agents also have been shown to cause loss of corneal epithelial cells in rabbit models. In contrast, formulations without BAK showed significantly less toxicity in rabbit corneal epithelial cells and immortalized human corneal epithelial cells.

Two recently published studies[8,9] by Kahook and Noecker further illustrate the negative effects of BAK. In one study, to reflect clinical dosing of the prostaglandin medications, eyes of New Zealand white rabbits received 1 drop per day of either travoprost preserved with sofZia (Travatan Z, Alcon Laboratories Inc.), latanoprost ophthalmic solution preserved with 0.02% BAK (Xalatan, Pfizer Inc.) or preservative-free artificial tears. After 30 days, transmission electron microscopy revealed corneal tissue treated with either preservative-free artificial tears or travoprost preserved with sofZia exhibited similar changes. Significantly more corneal epithelial damage was noted with latanoprost than with BAK-free travoprost, and the number of lymphocytes in the conjunctival epithelium and stroma was significantly lower in eyes treated with BAK-free travoprost.

In the study[9] by Kahook and Noecker, in which New Zealand white rabbits were dosed in the same manner following enucleation, researchers used mucin stains to identify goblet cells, which were then quantified. The number of goblet cells in the latanoprost eyes was significantly lower than in the other two groups. In addition, researchers detected no statistically significant difference in goblet cell numbers between eyes receiving BAK-free travoprost and those receiving preservative-free tears.

Effects of BAK: Clinical Studies

Clinical studies also have implicated BAK as detrimental to ocular surface health. A crossover, randomized, double-blind study[10] by Baudouin and colleagues found that BAK-preserved carteolol ophthalmic solution (Ocupress, Bausch & Lomb) significantly reduced tear breakup time (TBUT) from baseline at 3 hours and 3 days after instillation in the eyes of healthy volunteers. In the same study,[10] the tear film of healthy eyes dosed with preservative-free carteolol was more stable.

By Clark L. Springs, M.D., and Richard S. Davidson, M.D.

In addition to short-term effects, such as the TBUT decrease observed by Baudouin,[11] BAK can have long-term effects on the human ocular surface, such as inflammatory changes. Baudouin and colleagues[11] have observed that the conjunctiva of patients not using topical glaucoma medications contained only the occasional human leukocyte antigen (HLA DR)-expressing cell, whereas 92% of those using multiple medications for more than a year were abnormally infiltrated by inflammatory cells or fibroblasts.

A number of in vitro studies, as well as analyses of conjunctival biopsy specimens, similarly have indicated that the negative effects of BAK-preserved glaucoma medications are more significant when we treat patients with higher doses or for longer periods of time.[12–14]

Not all studies, however, have reported similar, negative effects of BAK-preserved medications on the ocular surface. In one of the largest double-masked, randomized, multicenter clinical trials[15] that compared BAK-free travoprost to travoprost preserved with BAK, the most frequently reported, treatment-related adverse event over 3 months was ocular hyperemia. Researchers reported ocular hyperemia in 6.4% of patients in the BAK-free travoprost group and 9.0% in the BAK-preserved travoprost treatment arm. Although the frequency of ocular hyperemia was lower in patients who used BAK-free travoprost, the difference in the two groups wasn't statistically significant. Four patients in the BAK-preserved travoprost group reported mild corneal staining vs. one patient in the BAK-free travoprost arm.

The results of this study may have departed from other clinical trials that have shown the negative effects of BAK-preserved medications on the ocular surface because patients with preexisting ocular surface disease would have been excluded, and perhaps the 3-month duration wasn't sufficient enough to identify significant corneal toxicity. It's also possible that other factors may contribute to corneal toxicity seen in glaucoma patients treated with prostaglandin analogues.

A prospective, randomized double-masked study[16] by Gross and colleagues that compared the duration of action of travoprost with BAK to travoprost without BAK found that both formulations had similar efficacy and safety profiles. Side effects were uncommon, mild in intensity and comparable in both groups.

Impact of BAK

All BAK-induced ocular surface changes, including a decrease in TBUT, a reduction in epithelial cell integrity, an increase in conjunctival inflammatory cells or loss of goblet cells, are part of the cascade of events whose final common pathway is OSD. As defined by the International Dry Eye WorkShop (DEWS), in its 2007 report,[17] dry eye/OSD is "a multifactorial disease of the tears and ocular surface," accompanied by increased tear film osmolarity and inflammation.

The DEWS report further explained how dry eye/OSD results in "symptoms of discomfort and visual disturbance." Many studies have underscored the significant impact of OSD on a patient's quality of life. For example, when utilities (patients' preferences) for OSD were compared with those for other diseases, severe OSD fell in the same range as class III/IV angina.[18] OSD also has been linked to measurable difficulties with common and important tasks of daily living, such as reading, using a computer, watching television and driving.[19]

Two factors of particular importance for glaucoma patients are the potential for ocular discomfort that leads to noncompliance with prescribed IOP-lowering medication use and the increased risk of trabeculectomy failure due to inflammation.[20]

Diagnosing OSD

The approach to diagnosing OSD in glaucoma patients, as in all patients, should be systematic. In addition, because topical medications preserved with BAK may be exacerbating or even causing ocular surface problems in this population, the history should include a patient's current medication use.

At the slit lamp, the clinician should examine the eyelids to determine if they're properly positioned, not inverted or everted. The blink should be evaluated for complete closure. The appearance of the tear film and conjunctiva and the presence of anterior chamber inflammation should be noted. Close inspection of the lids and lashes can reveal signs of anterior blepharitis, which often coexists with and contributes to OSD. Collarettes at the lash base indicate the presence of a *Staphylococcus* infection; sleeves indicate problems with the sebaceous glands or *Demodex folliculorum*.

Detection of posterior blepharitis, a frequent cause of lipid layer dysfunction and evaporative tear loss, hinges on close examination of the meibomian glands. You should note the presence or absence of telangectasia and metaplasia and express the glands. Thick or viscous meibum signals a problem that must be addressed.

The Schirmer's test can aid assessment of the aqueous layer of the tear film. It's a specific test of tear production, but it has low sensitivity. It's helpful mainly for determining whether or not aqueous tear deficiency is playing a role in OSD. Less than 10 mm of wetting after 5 minutes is indicative of dry eye/OSD.

The innermost layers of the tear

film, mucin and glycocalyx, are produced by goblet cells. Lissamine green staining reveals cells that are lacking the protective mucin and glycocalyx coating (**Figure 1**). In later stages of OSD, fluorescein staining reveals areas where epithelial cells are missing (**Figure 2**). Observation of the staining patterns also is helpful for diagnosis and treatment. With OSD, staining is usually concentrated in the lower cornea and bulbar conjunctiva. With ocular surface problems more closely related to toxicity, staining is more diffuse, over the entire cornea, and it also may appear under the eyelids.

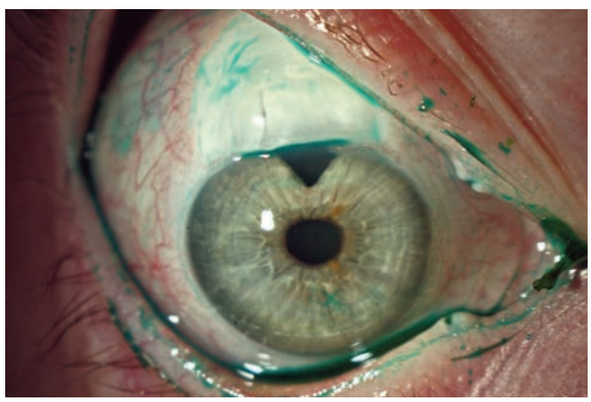

Figure 1. Lissamine green dye shows staining consistent with ocular surface disease in a patient who has undergone a trabeculectomy.

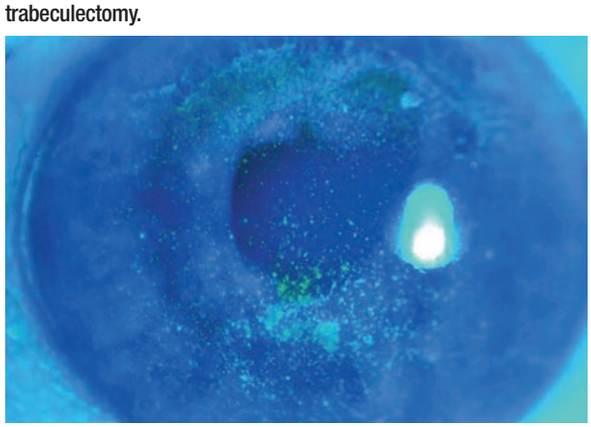

Figure 2. Fluorescein staining reveals punctate epithelial erosions in a glaucoma patient with ocular surface disease.

Although TBUT isn't a specific measure of tear film abnormality, it's highly sensitive. Normal TBUT is 6 to 10 seconds. The faster the TBUT, the longer the ocular surface goes unprotected, and the more likely the inflammatory cascade of dry eye/OSD will begin.

In addition to clinical signs, patient-reported symptoms are an important factor for prompting a thorough OSD evaluation. The OSDI, a 12-question survey and scoring system frequently used in OSD-related clinical trials, is useful in clinical practice as well. It has been validated[21,22] and can be used to support the diagnosis of OSD and to monitor response to treatment.

Treating OSD

Because glaucoma is a chronic disease, requiring ongoing topical therapy in nearly all cases, clinicians should take into account the long-term effects of each treatment. When possible, the first step in treating OSD in patients with glaucoma should be removing any BAK-containing medications from the patient's treatment regimen.

The 2007 DEWS Report[17] supports this strategy in all cases of OSD with its statement: "The single most critical advance in the treatment of dry eye came with the elimination of preservatives, such as benzalkonium chloride (BAK), from OTC lubricants." Furthermore, an increasing number of ophthalmologists are observing the benefits of removing BAK-preserved medications from the treatment regimen of glaucoma patients with OSD. Results appear to depend on the severity of signs and symptoms at baseline, but significant changes in TBUT, corneal staining and symptoms have occurred in a matter of weeks for some patients.

The effect of decreasing glaucoma patients' exposure to BAK also has been formally studied. Peace and colleagues[23] recently published results of a prospective, multicenter, historical controlled study of patients previously treated with BAK-preserved latanoprost or bimatoprost (Lumigan, Allergan Inc.), who were switched to travoprost preserved with sofZia.

After 3 months, the patients demonstrated a clinically and statistically significant reduction in OSD symptoms. Areas that improved on the OSDI included sensitivity to light, grittiness, pain, blurred or poor vision, difficulty reading and driving at night, doing computer work and discomfort in windy and low-humidity conditions. Patients also experienced statistically significant improvements in IOP, conjunctival hyperemia and visual acuity. An analysis of patients' preferences showed that 72.4% of the 691 subjects who completed the study preferred BAK-free travoprost.

Horsley and Kahook[24] presented results from a prospective, consecutive case series involving 40 eyes of 20 patients who were switched from monotherapy with BAK-preserved latanoprost to sofZia-preserved travoprost. Entry criteria included TBUT less than 6 seconds. Patients' OSDI scores and TBUT were reevaluated 6 to 8 weeks after they switched medications. At that time, mean TBUT increased from 2.02 seconds ± 0.71 to 6.34 seconds ± 1.31; OSDI scores decreased from 26.31 to 16.56.

Initiating Additive Therapy

Based on the available evidence, ophthalmologists should recognize that

medications containing BAK are contributing to OSD and, whenever possible, avoid prescribing them for glaucoma patients, who are uniquely susceptible. They also should switch patients already using BAK-preserved medications to drops containing gentler preservatives or no preservatives. Such a strategy is possible today because more options, with efficacy equivalent to BAK-preserved medications, are available. The availability of travoprost with sofZia, a gentler preservative, is an especially notable development given the widespread use and superior efficacy of the prostaglandin class of IOP-lowering drugs.

Once the baseline health of the ocular surface is determined, without the effects of BAK, you can initiate further treatment in line with current thinking and practice.[25] Based on severity of signs and symptoms, you can add the appropriate treatment options. **OM**

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Stepwise Approach Stabilizes Ocular Surface For Glaucoma Patient

Learn how a glaucoma patient with a variety of ocular surface conditions found relief and a better quality of life.

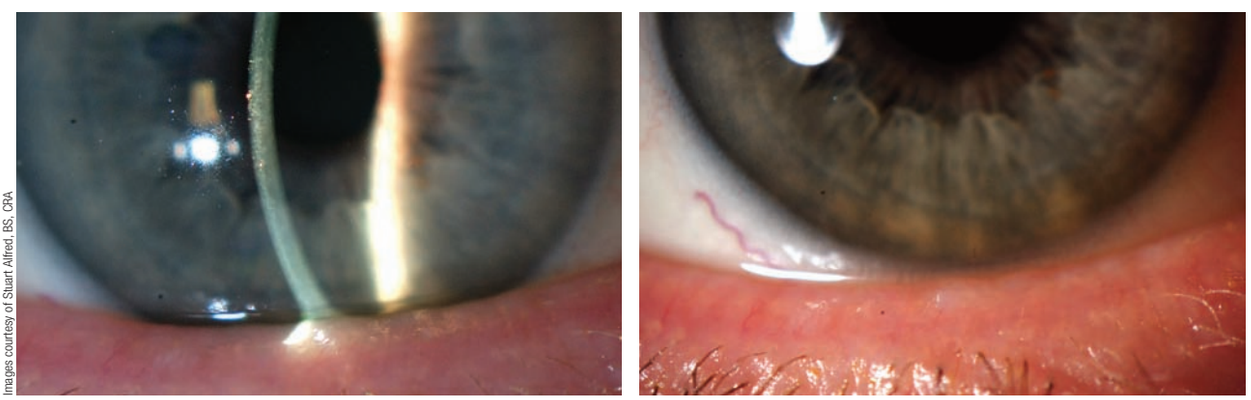
Ocular surface disease (OSD) is a common problem among patients with glaucoma, and its prevalence in this group may be much higher than in the general population.[1] Left untreated, OSD can lead to severe ocular discomfort because of dry eye symptoms, decreases in visual function, intolerance of topical glaucoma therapies and, as the previous article explained, chronic, harmful changes to the ocular surface.

The case described here, involving a 65-year-old Caucasian man with advanced open-angle glaucoma, is representative of the clinical challenge that glaucoma patients with OSD present. It also illustrates therapeutic strategies that have been successful in stabilizing the tear film and restoring a healthier, more comfortable ocular surface in this group of patients.

Patient History and Examination

In addition to having open-angle glaucoma in both eyes, this patient has a history of rosacea and posterior lid margin disease (**Figure 1**). He was referred to our group of cornea specialists after reporting reduced vision OU. His IOP was controlled (in the low teens) with the use of latanoprost ophthalmic solution (Xalatan, Pfizer Inc.) once daily, a fixed combination of dorzolamide hydrochloride and timolol maleate ophthalmic solution (Cosopt, Merck & Co. Inc.) twice daily and brimonidine tartrate ophthalmic solution 0.1% (Alphagan P, Allergan) twice daily. His lid margin disease had been controlled with 50 milligrams of doxycycline twice daily, an Omega-3 oral supplement (1 g) once daily, a lid hygiene regimen and preservative-free artificial tears. However, his cardiologist had recently diagnosed him with atrial fibrillation and prescribed warfarin (Coumadin, Bristol-Meyers Squibb) to reduce the associated risk of stroke and blood clots in the heart. The doxycycline and warfarin were interacting and interfering with the patient's PT/INR (prothrombin time/international normalized ratio) test results. Therefore, the cardiologist recommended that we discontinue doxycycline.

We first saw the patient 6 weeks after we discontinued the doxycycline, and his best-corrected visual acuity had decreased from 20/20 to 20/30. Also, a slit lamp exam showed lid telangiectasia and inspissated meibomian glands. We performed a Schirmer's test, and tear production was normal (15 mm of wetting in 5 minutes). However, tear film break-up time (TBUT) was below normal OU, at 3 seconds. (See "Performing the TBUT Test.")



Images courtesy of Stuart Alfred, BS, CRA

Figure 1. A patient with open-angle glaucoma presented with a history of rosaea (shown here), which exacerbated his ocular surface disease symptoms, such as reduced vision OU and lid margin disease — characterized by lid telangiectasia and inspissated meibomian glands.

By Clark L. Springs, M.D.

Treatment Plan

Because the preservative benzalkonium chloride (BAK) has been shown to contribute to OSD, our first step was to discontinue latanoprost, which contains BAK, and prescribe travoprost with sofZia (Travatan Z, Alcon Laboratories), a gentler preservative. SofZia is believed to be less irritating and less toxic to the ocular surface than BAK.[2–6]

After 6 weeks of using travoprost with sofZia, the patient's visual acuity improved from 20/30 to 20/25, but he expressed continuing concern about the quality of his vision. At this visit, we prescribed topical cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan). After an additional 6 weeks, the patient's visual acuity returned to 20/20, and his TBUT improved to 7 seconds. Moreover, his IOP remained unchanged at 12 mm Hg to 14 mm Hg. We've seen this patient several times since that visit. He's continued using cyclosporine and travoprost with sofZia and has no complaints related to OSD. His IOP has been stable in both eyes.

Discussion

Several key points can be drawn from this case:

- Both warfarin and doxycycline are protein-bound drugs; therefore, it's important for ophthalmologists to be aware of the fact that they can interact unfavorably.
- When glaucoma patients develop signs and symptoms of OSD, it's usually helpful to remove BAK-containing medications whenever possible, so you don't compromise IOP control.
- While removing BAK-preserved medications from patients' treatment regimens is often helpful, other steps may be necessary in order to normalize the ocular surface.
- Therapeutic changes should be prescribed one at a time so you can adequately evaluate their effects.
- In the interest of patient compliance, switching to a medication that's less harmful to the ocular surface is preferable to adding a medication to the existing regimen. **OM**

Performing the TBUT Test

While many clinicians use a fluorescein drop, such as fluorescein sodium and benoxinate hydrochloride (Fluress, Akorn Inc.), to perform TBUT testing, I prefer to use a fluorescein strip. Most drops are instilled at volumes ranging from 20 µL to 40 µL, which I believe to be an inordinate amount. It takes several minutes for that much volume to clear before you can make an accurate assessment of the TBUT. Also, the drops often contain anesthesia, which can prevent the patient from blinking naturally, skewing the test results.

I moisten the fluorescein strip with one drop of a preservative-free artificial tear and place it on the lower lid until the dye adequately spreads over the ocular surface. I instruct the patient to blink naturally several times and then look straight ahead without blinking. Using diffuse cobalt blue slit lamp lighting and low magnification, I count the number of seconds between the last complete blink and the first appearance of a dry spot or discontinuity in the tear film.

Many clinicians also use a Wratten yellow filter to observe the TBUT. While this may be necessary when TBUT testing is part of a clinical trial, I have found it's not necessary in everyday clinical practice.

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Ophthalmology Management

Managing Ocular Surface Disease in the Glaucoma Patient October 2008

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Please select the single best answer and indicate your choice on the Evaluation Form on the next page.

1. In a recent study by Robert D. Fechtner, M.D., and colleagues, what percentage of patients being treated for glaucoma had an Ocular Surface Disease Index (OSDI) score of mild, moderate or severe?
a. Nearly 20%
b. Nearly 30%
c. Nearly 40%
d. Nearly 50%

2. The most common beta-adrenergic antagonist solution is 0.5% timolol and what percentage of other substances?
a. 99.5%
b. 89.5%
c. 79.5%
d. 69.5%

3. When Dr. Fechtner and David S. Chu, M.D., switched an 83-year-old woman with open-angle glaucoma from dorzolamide hydrochloride (Trusopt, Merck & Co. Inc.) to travoprost with sofZia (Travatan Z, Alcon Laboratories Inc.), the change eliminated the benzalkonium chloride (BAK) and reduced the patient's total drop burden to how many drops per day?
a. 1 drop
b. 2 drops
c. 3 drops
d. 4 drops

4. Which medication containing BAK did Richard S. Davidson, M.D., discontinue in a 58-year-old woman with a 9-year history of open-angle glaucoma in favor of travoprost preserved with sofZia?
a. Bimatoprost (Lumigan, Allergan)
b. Latanoprost ophthalmic solution (Xalatan, Pfizer Inc.)
c. Brimonidine tartrate ophthalmic solution 0.1% (Alphagan P, Allergan)
d. Dorzolamide

5. Which of the following is associated with BAK, a detergent-type preservative used in most topical ophthalmic medications?
a. Reduced microbial contamination
b. Ocular surface irritation
c. Corneal cell death over time
d. All of the above

6. According to a study by Kahook and Noecker, which compared travoprost with sofZia to latanoprost preserved with 0.02% BAK and preservative-free artificial tears, what was the effect of these agents after 30 days on the number of lymphocytes in the conjunctival epithelium and stroma?
a. Significantly lower in eyes treated with BAK-free travoprost
b. Significantly higher in eyes treated with BAK-free travoprost
c. The numbers did not differ significantly.
d. These factors were not measured.

7. In another study of the same three agents, Kahook and Noecker found the number of goblet cells was significantly lower in eyes treated with which of the following?
a. Travoprost preserved with sofZia
b. Latanoprost preserved with 0.02% BAK
c. Preservative-free artificial tears
d. The numbers did not differ significantly.

8. In a study by Baudouin and colleagues, which of the following agents significantly reduced tear breakup time (TBUT) from baseline at 3 hours and 3 days after instillation in the eyes of healthy volunteers?
a. Travoprost preserved with sofZia
b. Latanoprost preserved with BAK
c. Carteolol ophthalmic solution (Ocupress, Bausch & Lomb) preserved with BAK
d. Preservative-free artificial tears

9. According to which of the following, when patients' preferences for ocular surface disease (OSD) were compared with those for other diseases, severe OSD fell in the same range as class III/IV angina?
a. Ocular Surface Disease Index
b. International Dry Eye WorkShop
c. Ocular Hypertension Treatment Study
d. Schiffman and colleagues

10. According to Clark L. Springs, M.D., and Richard S. Davidson, M.D., which of the following tests is helpful mainly for determining whether or not aqueous tear deficiency is playing a role in OSD?
a. Schirmer's
b. Lissamine green
c. Tear breakup time
d. Fluorescein staining

11. According to Drs. Springs and Davidson, which of the following should be the first step in treating OSD in patients with glaucoma?
a. Trabeculectomy
b. Removal of BAK-containing medications from the treatment regimen
c. Incremental reduction of the BAK load
d. Referral to a cornea specialist

12. According to a prospective, multicenter, historical controlled study by Peace and colleagues, what percentage of 690 patients preferred BAK-free travoprost to BAK-preserved latanoprost or bimatoprost?
a. 32%
b. 52%
c. 72%
d. 92%

13. A cardiologist of a 65-year-old patient with advanced open-angle glaucoma and atrial fibrillation suggested that Dr. Springs discontinue which of the following antibiotics that interacted with the anticoagulant warfarin (Coumadin, Bristol-Meyers Squibb)?
a. Tetracycline
b. Minocycline
c. Doxycycline
d. Methacycline

14. After the 65-year-old patient with advanced open-angle glaucoma used cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) for 6 weeks, his tear film breakup time improved to how many seconds?
a. 3 seconds
b. 5 seconds
c. 7 seconds
d. 9 seconds

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Ophthalmology Management

Managing Ocular Surface Disease in the Glaucoma Patient October 2008

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Answers (Refer to questions on previous page.) Circle one letter for each answer.

1.	A	B	C	D	**6.**	A	B	C	D	**11.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D	**12.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D	**13.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D	**14.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D					

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PROGRAM EVALUATION — Please rate with a numeric value when applicable.
Did this program meet the following educational objectives? 5 = Strongly Agree, 1 = Strongly Disagree

A. Can you recognize the prevalence of ocular surface disease in glaucoma patients?

B. Do you understand the long-term effects of glaucoma medications on the ocular surface?

C. Can you discuss recent research linking an increase in ocular surface disease to IOP-lowering medications containing benzalkonium chloride (BAK)?

D. Have you learned how to assess, treat and manage ocular surface disease while monitoring the effects of glaucoma therapy?

What was the overall level of commercial bias? 5 = High commercial bias, 1 = Low commercial bias

Comments regarding commercial bias:

Rate your knowledge/skill level prior to attending this course: 5 = High, 1 = Low

Rate your knowledge/skill level after attending this course: 5 = High, 1 = Low

Would you recommend this program to a colleague? ❑ Yes ❑ No

Do you feel the information presented will improve/change your patient care? ❑ Yes ❑ No
If yes, please specify

May we contact you by e-mail in 3-4 months to see if you have made this change? ❑ Yes ❑ No

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