

Supplement to

Glaucoma

TODAY

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Glaucoma Medications and Their Effects on the Corneal Surface

A roundtable discussion.

FEATURING:

Ronald Gross, MD, Moderator

Malik Y. Kahook, MD

Shan Lin, MD

Robert J. Noecker, MD, MBA

Stephen C. Pflugfelder, MD

Jointly sponsored by The Dulaney Foundation and *Glaucoma Today*.

This continuing medical educational activity is supported by an unrestricted educational grant from Alcon Laboratories, Inc.

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STATEMENT OF NEED

Many patients with glaucoma have concurrent ocular surface disease. Ophthalmologists therefore must look for problems of the ocular surface and consider options for its improvement that will not compromise the treatment of glaucoma. A healthy ocular surface can improve patients' comfort and lower the risk of failed filtering surgery in the future.

TARGET AUDIENCE

This activity is designed for ophthalmologists.

LEARNING OBJECTIVES

After the successful completion of this program, the participant should be able to:

- Explain the role of benzalkonium chloride in glaucoma medications;
- Describe the potentially deleterious effects of benzalkonium chloride on the ocular surface;
- Identify which patients are at particular risk for an

adverse reaction to benzalkonium chloride; and

- Discuss the possible benefits of transitioning the patient from a glaucoma medication preserved with to one preserved without benzalkonium chloride.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. This test is available exclusively online at <http://www.CMEToday.net>. Once you register and log in, you can take the test, get real-time results, and print out your certificate. Please email gmcdermott@bmctoday.com or call (484) 581-1812 if you have any questions or technical problems with the Web site.

Upon completing the activity and achieving a passing score of 70% or higher on the self-assessment test, participants can print out a CME credit letter awarding

AMA PRA Category 1 Credit™. The estimated time to complete this activity is 2 hours.

ACCREDITATION

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and Bryn Mawr Communications LLC, publisher of *Glaucoma Today*. The Dulaney Foundation is accredited by the ACCME to provide CME for physicians.

The Dulaney Foundation designates this educational activity for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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FACULTY DISCLOSURE DECLARATIONS

Ronald Gross, MD, is a consultant to Alcon Laboratories, Inc., and Allergan, Inc. He has received grant/research support from and is on the speakers' bureaus of Alcon Laboratories, Inc., Allergan, Inc., Merck & Co., Inc., and Pfizer Inc.

Malik Y. Kahook, MD, has received grant/research support from Alcon Laboratories, Inc., Allergan, Inc., Pfizer Inc., and Merck & Co., Inc., and he is on the speakers' bureaus of Alcon Laboratories, Inc., and Allergan, Inc.

Shan Lin, MD, indicated that he has no financial arrangement or affiliation with any manufacturers' products or providers of service mentioned in this activity.

Robert J. Noecker, MD, MBA, is a consultant to Allergan, Inc. He has received grant/research support from Allergan, Inc., Carl Zeiss Meditec, Inc., and Lumenis Inc., and he is on the speakers' bureaus of Allergan, Inc., Alcon Laboratories, Inc., Lumenis Inc., and Endo Optiks.

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MANAGING PATIENTS WITH GLAUCOMA

Gross: Given the large number of studies that have been published over the past 10 years, there are fairly consistent, unequivocal data that the treatment of glaucoma hinges on the practitioner's ability to lower IOP and that reducing the IOP decreases the risk of progressive glaucomatous damage (particularly visual field loss) for all types of glaucoma, including ocular hypertension, normal-tension glaucoma, and primary open-angle glaucoma (POAG). Obviously, our patients' compliance with the prescribed drug regimen is a factor in therapy's success.

In general, we can lower pressure by topical medications, laser trabeculoplasty, and filtration surgery. Given the risks and benefits of each approach, the vast majority of patients in the US choose to be treated with medical therapy. The available classes of agents include prostaglandin analogs, beta blockers, alpha agonists, and topical carbonic anhydrase inhibitors. Each has advantages and disadvantages that clinicians must understand in order to tailor therapy appropriately to each individual. In most cases, the prostaglandin analogs are now the mainstay of therapy, given their obvious benefits for lowering IOP (for which they are superior to any other class) and their safety profiles, with little in the way of any systemic safety concerns. As with any medication, these drugs do have some potential side effects, as we will discuss.

Noecker: I would agree that prostaglandin analogs are the de facto first-line agents and, if possible, the monotherapy of choice. Probably half of my patients need more than a prostaglandin, which is where the other classes of drugs come into play. Often, the patient will use his initial-prescribed medication for a long time.

Lin: There is evidence that the diurnal and long-term fluctuation of IOP can affect the progression of glaucoma.^{1,2} Moreover, data from Europe³ as well as some limited data from Liu et al⁴ show that prostaglandin analogs are better than topical beta blockers at controlling diurnal fluctuation.

Gross: We also need to keep in mind that glaucoma is a chronic disease and most patients will need lifelong treatment. Patients really treat themselves. They must be capable of complying with the regimen we give them. In addition, they have to instill the medication every day to ensure they get the best potential outcome. There are many factors that go into the decision as to which agent is best for them, but we have to keep in mind that they may have to follow the regimen for many years. The

impact on both the patients and their eyes should be taken into consideration.

What other considerations do we have to take into account to be successful in the long-term treatment of our patients?

Kahook: Ron and Rob have already indicated that monotherapy is probably the easiest for patients and likely improves adherence. In addition, we must consider a drug's potential effect on the ocular surface, especially among patients who are using more than one medication on a daily basis. The preservative load of various agents must be considered when patients complain about dry eyes, stinging, burning, and general discomfort. The available medications have varying concentrations of benzalkonium chloride (BAK) and affect the corneal epithelium differently. Minimizing the load of BAK in each patient is one step toward improving their comfort and adherence to prescribed therapy.

Gross: Steve, would you mind discussing BAK's potential effects on the ocular surface?

Pflugfelder: With regard to any topically applied medication, there is the toxicity from the medication itself, and there is the toxicity from the preservative system. It has become clear over the past few decades that BAK is a fairly toxic agent for the surface of the eye, even in fairly low concentrations.⁵ BAK is basically a detergent, so it has surfactant properties in relation to the eye. It has been known for a long time that it can disrupt corneal-barrier function. As a result, in the long run, BAK can cause corneal ulceration, superficial punctate epitheliopathy, decreased vision, and even stromal haze. Recently, French studies have demonstrated that BAK has pro-inflammatory effects.⁶

BAK increases the levels of inflammatory cytokines in the tear film as well as the levels of inflammatory cells in the conjunctival epithelium and the stroma.⁶⁻⁸ BAK also has intrinsic cell-membrane toxicity.⁵

When patients are using multiple medications, there is a cumulative effect of BAK, unless clinicians prescribe some of the newer drugs that have alternative preservative systems.

Gross: Some clinicians maintain that the presence of BAK can be advantageous, because it disrupts those epithelial barriers, allows greater penetration of the drug into the eye, and thus aids efficacy. Is that a misconception, or are there supporting data?

Pflugfelder: I think BAK does increase penetration, which could be good or bad. In the case of antimicrobials, deeper penetration could be advantageous, because it would increase the level of the drug in the ocular tissue and its concentration in the aqueous humor. In the case of post-operative medications, BAK may increase the risk of cystoid macular edema.⁹

Lin: Regarding glaucoma medications, I am aware of two studies on whether BAK affects IOP lowering in the clinical setting. The first article was by Badouin and de Lunardo, who did not find a significant difference in efficacy between preserved and unpreserved carteolol.¹⁰ A more recent study with travoprost ophthalmic solution with BAK (Travatan; Alcon Laboratories, Inc., Fort Worth, TX) and with the new formulation preserved without BAK (Travatan Z; Alcon Laboratories, Inc.) showed that they were statistically equivalent to each other in their reduction of IOP.¹¹

Kahook: The idea that the penetration of glaucoma medications into the anterior chamber requires BAK is now outdated. BAK was first used as a preservative with less lipophilic medications than we currently have. Today's agents do not need a break in the cell-to-cell adhesions in order to pass through the epithelium and endothelium of the cornea.

In addition to the side effects mentioned by Steve, I would like to comment that BAK has acute and chronic effects. As a detergent, it disrupts the tear film after just a single drop.¹⁰ With the extended or chronic use of preserved medications, BAK's effect extends to the cells that are producing the first layer of the tear film—namely, the goblet cells. With fewer goblet cells and a decreased production of mucin, the tear film becomes unstable and incapable of maintaining a healthy ocular surface. A breakdown in the superficial cellular layer and conjunctival inflammation soon ensues.

Noecker: BAK is a preservative system that was introduced into ophthalmic medications back in the 1950s. It is also a surfactant that stabilizes some of these drugs in solution. An important point is that all glaucoma medications are not equal in their amount of BAK. The amount can vary greatly. Some drugs need higher amounts of BAK in the formulation to keep them in solution. I think that is part of the puzzle.

Research published in the 1990s identified the number of medications that the patients were using and correlated that to conjunctival inflammation. There was no mention of BAK, and the investigators attributed a lot to the mecha-

nism and subtype of the drug. The big offenders were miotics and epinephrine compounds.¹² Research shows that the drugs we use today contain fairly benign active compounds.⁸ There really does seem to be a vehicular problem, BAK, which is the big offender we are talking about today.

Gross: The question is, if we are only talking about one drop a day, how much difference can that really make?

Pflugfelder: I think it depends on a lot of factors. The age of the patient is one, and most individuals with glaucoma are older. A lot of them have some dry eye or other ocular surface problems, and they are more susceptible to these conditions.¹³ Instilling a single BAK-containing drop in the eye of a 20-year-old with excellent tear function and reflex tearing will not make a difference. The same drop for a 70-year-old with dry eye or punctal stenosis will produce a higher concentration of the drug in the ocular tissue, and the eye will be more susceptible to toxicity.

Gross: How often do we have to worry that one drop will make a difference to patients who have a compromised ocular surface?

Pflugfelder: Epidemiologic studies have shown that 15% of the population aged 65 and older have a dry eye,¹³ and that rises with increasing age. In the seventh decade of life, the incidence of dry eye increases to about 20%, whereas, in 80-year-olds, it may be as high as 30%.

Kahook: I do not think that any of the medications that are popular today have a benign concentration of BAK. Unfortunately, most of the data we have to support the fact that they are not benign come from in vitro studies that analyzed what BAK does in cell cultures as far as creating inflammatory cytokines or actually causing cellular apoptosis.¹⁴

We need to confirm these findings with more human studies. There are some convincing data that show that 0.005% of BAK in any of the medications can cause significant changes, even just with daily dosing.⁸

Gross: Glaucoma is more common in the elderly, among whom ocular surface disease is more common, as Steve has pointed out. Practitioners must recognize that the interaction of the two factors can have a synergistic effect on the patient's ocular surface and health.

Noecker: In truth, we prescribe drugs containing BAK every hour of the clinical day, and we cannot say we are

harming everyone. Now, we have some choices in agents' preservative systems.

I have instilled all of the available drops in my own eyes. Often, I experienced a short-term problem such as foreign-body sensation, which was probably due to a decrease in my tear film breakup time. People who are at risk of adverse effects from BAK include dry eye patients, with the classic signs of decreased tear film production. People who have preexisting conditions are the easiest ones to identify. A lot of older women have dry eyes. A lot of older men have acne rosacea and more meibomian gland disease. Clinicians must conduct a risk/benefit analysis for each patient.

Lin: When assessing patients for ocular surface disease and dry eyes, I look for epithelial keratopathy and assess their tear film breakup time. If I have a greater suspicion, I may test their rate of tear production as well as look at their corneas with fluorescein. I think that 40% to 50% of my patients have either dry eye syndrome or ocular surface disease.

Kahook: I think part of the problem is that there have been limited options when you identify a patient who has surface disease or dry eye or who complains about ocular stinging or burning or visual changes or fluctuations. Physicians have responded by prescribing artificial tears or anti-inflammatory medications or by placing punctal plugs, because little else could be done. The challenge is not only detecting ocular surface disease in the patients we see. We must also consider whether a BAK-free option might be appropriate and take the next step of removing as much BAK as possible from their drug regimen.

Pflugfelder: Identifying these patients is tough in a busy practice. One strategy is to teach your technicians to screen for these individuals. Because many have altered corneal sensitivity, their eyes may look horrible, but they may not complain of ocular irritation. A tip-off, however, is if they tell the technician that their eyes are scratchy, burn, or are red or if they complain of blurred or fluctuating vision. Unfortunately, many of the diagnostic tests for dry eye should be conducted before any drops are placed in the eye. When patients have received fluorescein containing anesthetic drops or their corneas have been applanated before the specialist sees them, it is difficult to make a diagnosis of dry eye. Ideally, a fluorescein strip moistened with unpreserved saline should be used to assess the patient's tear breakup time and the degree of corneal fluorescein staining prior to instilling any anesthetic drops.

The worst scenario is a patient who has horrible corneal epitheliopathy and a drop in visual acuity from 20/20 to 20/50 due to his glaucoma drops. Such a patient typically presents to my practice at least once a month.

Gross: Would you say a reasonable screening approach would be to flag patients if they complain of burning, if they use artificial tears, if they have evidence of corneal epithelial staining after the instillation of fluorescein, or if they exhibit tear breakup during the slit-lamp examination?

Pflugfelder: Yes, it would be. To be honest, I think most elderly glaucoma patients are going to have a rapid breakup time of 7 seconds or less, which shows that they all probably have a subclinical dry eye. I would say that the presence of fluorescein staining in the midperipheral or central cornea is the most specific sign that they have a dry eye or preservative-related toxicity.

Gross: Would any corneal staining represent an abnormality in the ocular surface? I mean a normal cornea does not have corneal epithelial staining with fluorescein.

Pflugfelder: That is correct. Normal corneas may have a little fluorescein staining inferiorly. If they have any more than that, the patient should be considered to have a dry eye.

Noecker: I have found that an effective screening strategy is just to ask if patients use artificial tears. If their eyes bother them enough that they went to the pharmacy and bought something, that is a good indication that we should pay attention to their ocular surface and consider their drug regimen.

Gross: What do we do with this patient? We have identified him as someone who may well have an ocular surface problem. He obviously needs treatment for his glaucoma. What is the most reasonable way to proceed?

Pflugfelder: I think these patients need to be managed by glaucoma and corneal specialists, because there are the issues of (1) controlling their IOP and keeping them from going blind from glaucoma and of (2) restoring ocular comfort and preserving their visual function. Many of the patients Ron and I share are monocular; if their visual acuity drops to 20/40, they are in big trouble. We have to get to the root cause of their symptoms, which is the toxicity from preservatives most of the time. You can try to mask the problem by treating patients with artificial tears or pre-

scribing an anti-inflammatory agent. Probably the worst treatment option for these patients is punctal occlusion, because that will worsen their tear turnover and make them even more susceptible to the preservative's toxicity. We have to work together to develop a treatment plan that will minimize or eliminate preservatives yet still control their IOP.

Noecker: As a corollary, treating the dry eye first or at least optimizing the ocular surface is beneficial. I think artificial tears, especially those without BAK, are still appropriate. It is not a simple problem. It is multifactorial. These patients tend to present with this underlying condition, which we tend to make worse with our therapies. On one hand, we can back off and lower the amount of BAK. Often, they still have an underlying condition.

Pflugfelder: I agree that it is a two-tiered approach. When I have just tried to treat the dry eye in the majority of these patients without addressing the issue of preservatives, I have gotten maybe a 10% improvement. If I address both, I may achieve a 50% to 70% improvement.

Lin: I want to mention some specific alternatives we have used in the past. I used formulations of timolol maleate that were preservative free (Timoptic Sterile Ophthalmic Solution; Merck & Co., Inc., Whitehouse Station, NJ; also specially formulated by Leiter's Pharmacy, San Jose, CA), which are not widely available and incur greater expense. Now, we have the new formulation of travoprost, which may allow us to get away from BAK as a primary preservative. As has been mentioned during our discussion, the effect of BAK is not an all-or-none proposition. The longer a patient uses it, the more it will affect his ocular surface and conjunctiva.

Gross: There is also brimonidine tartrate ophthalmic solution (Alphagan P; Allergan, Inc., Irvine, CA), which has a preservative system other than BAK. The new formulation of travoprost carries the positives (efficacy and safety) of the class of prostaglandin analogs but without the BAK. Comparative data have shown that both formulations of travoprost are equally efficacious throughout the day and for up to 60 hours.¹⁵

Noecker: That is an important point. It appears that we do not need BAK to treat glaucoma. Shan has alluded to a study in which the IOP-lowering effect was shown not to be adversely affected by a lack of BAK.¹⁰ You do not need BAK in terms of efficacy. No study has ever shown that a BAK

drug lowers IOP better than a non-BAK drug. Historically, we have continued to use BAK because of a lack of alternatives. I think we are entering a different era. BAK has been removed from most newer artificial tears.

Kahook: If BAK is not necessary to a drug's penetration into the anterior chamber, is it needed as a preservative? Is it more effective than existing alternatives? Presented data showed that oxidizing preservatives such as Sofzia (Alcon Laboratories, Inc.) are effective and meet USP Preservative Effectiveness standards.¹⁶ I think this suggests a shift away from detergent-type preservatives such as BAK, which are more harmful to the ocular surface.

Noecker: BAK is an effective preservative, and that is why it is still used. It appears that oxidizing compounds such as the ionic buffered preservative system used in the new formulation of travoprost are similarly effective. BAK is a potent preservative, but this comes at some cost in the clinical setting.

Gross: Would it be reasonable, desirable, or appropriate to use a glaucoma medication that does not contain BAK for a patient with manifestations of ocular surface disease? Switching everyone who has ocular surface disease from a BAK-containing prostaglandin analog to the new formulation of travoprost will produce an immediate, manifest improvement in the signs and/or symptoms of ocular surface disease in only some patients. To a certain extent, the transition involves a leap of faith by practitioners that they are prescribing a more benign course over the long term.

Pflugfelder: I find that such patients, in addition to discontinuing their BAK-containing agent, may require a 1- to 2-week course of an unpreserved steroid. Although this agent may exacerbate their glaucoma, it will get rid of the ocular redness. BAK may have adversely affected the corneal stem cells of some of these patients. In a couple of these individuals, I have observed a whorl-patterned corneal epitheliopathy that indicates that their stem cells have been damaged or traumatized, and it will take months for them to get better. It could be weeks or even months until you really see the effect of discontinuing the BAK-preserved drug. From that point on, however, you are going to be doing the patient a service.

Gross: Let me give you three scenarios, and I would like your comments. The first patient is using a BAK-preserved prostaglandin. He instills artificial tears b.i.d. and has no signs of ocular surface disease as far as staining.

The second patient uses more artificial tears more frequently but is symptomatic. The third uses cyclosporine ophthalmic emulsion and artificial tears and has a horrible ocular surface.

Does it make sense to switch an asymptomatic patient who uses artificial tears minimally from a medication preserved with BAK to one that is not? I think we would all agree that such a switch is warranted in the second and third patients I described.

Pflugfelder: The first patient is the one at risk. The physician will have to deal with the long-term complications of BAK down the road if a filtering procedure or a corneal transplant is required, procedures where abnormal wound healing may negatively impact the outcome. If a patient may need filtering surgery in the future or has other ocular problems, I think you should switch him to a non-BAK formulation at some point.

Gross: What if filtration surgery will not be likely?

Pflugfelder: I think the evidence suggests that you probably should anyway, but it is a tough call.

Kahook: I do not see it as a tough call. The literature and my laboratory experience show that BAK has a deleterious effect on the surface epithelium. Studies have shown that patients do not do as well after trabeculectomy when previously exposed to chronic doses of BAK.¹⁷ Because we cannot predict which patients may or may not need to have surgery in the future, it seems prudent to make the switch away from BAK when all else is equal.

Lin: I have a patient similar to the first one Ron described except that he is symptomatic. I had him switch from the original to the new formulation of travoprost, and he improved. Even if a patient is symptom free, you might consider making the change. What are you losing, really?

Gross: For patients who are symptomatic but have no signs, what should we do besides switching them to an unpreserved glaucoma drop if they are already using unpreserved artificial tears?

Pflugfelder: The next step after artificial tears is instituting anti-inflammatory therapy, usually topical cyclosporine. It could be augmented with oral tetracyclines or topical steroids. In the case of a glaucoma patient, oral tetracyclines are a better choice than steroids as an adjunct to cyclosporine.

Gross: Is there the possibility that making the switch from the BAK-preserved prostaglandin analog to one that is not will improve their symptoms? How long would you wait before you prescribed an anti-inflammatory?

Pflugfelder: Having followed patients for prolonged periods, I think that improvement will eventually happen in at least 50% of the patients. It is a dynamic process. The conjunctiva may have lost a lot of goblet cells, and it may take weeks for them to regenerate. Patients have to go through the whole cycle of replacement of the corneal epithelium, which will also take a while. Just changing the glaucoma drop may eventually take care of the problem.

Gross: How long should we wait?

Pflugfelder: I would say to give it 1 to 2 months, if the patient is willing to wait.

Gross: Would their normal visit in 3 or 4 months be adequate time to evaluate the impact of the switch?

Pflugfelder: Yes.

Noecker: Not to make generalizations, but I think a lot depends on how long the patients have been taking a drug. If they have used a drug with a high BAK content for a decade, I find that it takes longer to see improvement than if they only used the drug for 1 month before switching. It can take years for their ocular surfaces to return to what we consider normal. In some, change or improvement may be seen a lot earlier, but I would say that the person's ocular surface is still not in a normal state in that short a period of time. If I performed a biopsy at the time of trabeculectomy, I would probably find plenty of inflammatory cells.

To hasten recovery, as Steve said, I think you can prescribe anti-inflammatory therapy. Sooner or later, whatever we do fails. If you bought them a few years without BAK, that could be significant before you have to start adding adjunctive or alternative therapy with BAK.

Gross: Several people have alluded to the potential impact of BAK on filtration surgery and wound healing. Steve, please discuss the potential impact of BAK on ophthalmic surgery.

Pflugfelder: Ophthalmologists have long recognized the advisability of minimizing preserved drugs after corneal transplantation. It is tough, because there are no commercially available unpreserved steroids in the US. It is also

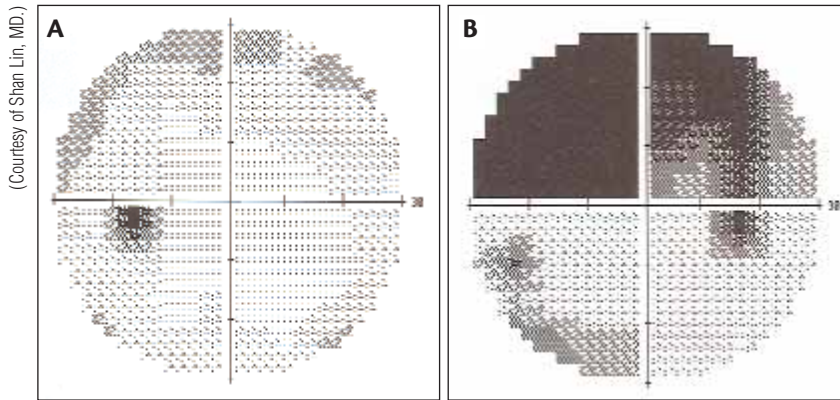


Figure 1. Humphrey visual field testing (Carl Zeiss Meditec, Inc., Dublin, CA) showed mild superior peripheral field loss in the left eye of the patient described in Case No. 1 (A). His right eye exhibited almost superior hemifield loss and a significant inferior arcuate defect (B).

advisable to minimize preserved medications after refractive surgery or any procedure that has a fairly large wound-healing component. In a patient who develops an epithelial defect or a recurrent corneal epithelial erosion, I try to avoid medications that contain preservatives. If the patient has glaucoma, which many of my cornea patients do, I would certainly consider using a glaucoma therapy that does not contain BAK.

Noecker: I used to say that pilocarpine posed the biggest risk for failed trabeculectomy. Now, I would say it is the vehicle of the drug and the duration and frequency of its use. Studies that were done initially only looked at the kinds and number of medications that were being used. With the increased use of more potent, newer medications with little or no BAK that are dosed less frequently, without a doubt, treated glaucomatous eyes quiet down faster than they did 10 or 15 years ago.¹⁸

Gross: Would you mind expounding a bit on the data?

Noecker: In 1994, Broadway and colleagues looked at patients on multiple medications containing BAK and the duration of therapy. The treatment options were totally different at that time, and timolol was probably the best medication available then. While today, timolol with BAK is probably

one of the bigger offenders against the ocular surface. The investigators correlated conjunctival inflammation with the prolonged use of miotics and epinephrine. Although it is hard to sort out other confounders of the disease state, trabeculectomy's success rate dropped off dramatically when patients were on multiple medications. I think we see that today with even the newer medications at times.^{12,18}

Kahook: We mentioned that BAK can decrease the success of a trabeculectomy. There are elegant studies showing that BAK may hasten the time to surgery by causing inflammation of the conjunctiva and trabecu-

lar meshwork.^{12,19}

Studies by Broadway et al^{20,21} and Sherwood et al¹⁸ have shown that the conjunctiva becomes inflamed after exposure to medications containing BAK and that treating patients with steroids prior to conjunctival biopsy decreases the lymphocytic load. In effect, by treating some of our patients with medications that contain high concentrations of BAK, we may be decreasing their chances of successful filtration surgery, if such intervention is needed in the future.

Lin: I agree that BAK probably leads to a greater rate and earlier failure of filtration surgeries. When I have talked to colleagues about this issue, some of them have raised the notion that the older studies that Rob was referring to were done in the days when mitomycin C (MMC) and other agents were not used as commonly as today. Now that we have MMC, do we really care if BAK is in the for-



Figure 2. The patient described in Case No. 1 had used timolol 0.5% (A). One month after adding the new formulation of travoprost, which is not preserved with BAK, the appearance of his eyes had not changed significantly, and the patient had no complaints about the medication (B).

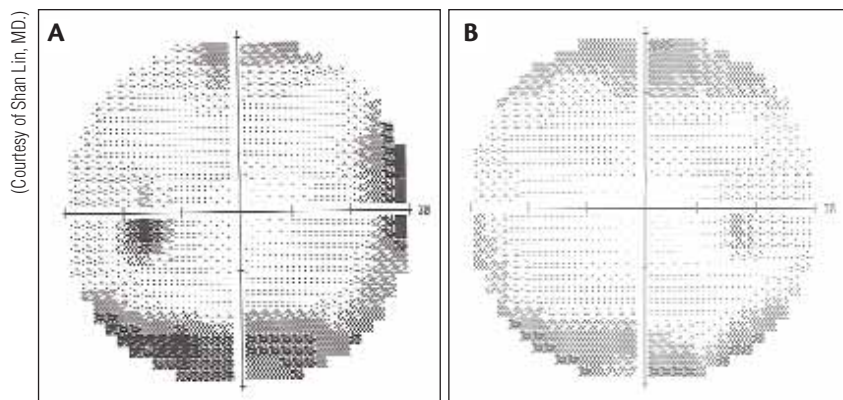


Figure 3. Visual field testing of the patient described in Case No. 2 revealed inferior and superior arcuate defects in his left eye (A) and more mild inferior and superior arcuate defects in his right eye (B).

mulation? Why are we using one toxic agent to combat another? We want to find ways to avoid the eye's exposure to MMC and prevent the agent's use over a long duration. MMC is a major contributor to our relatively high complication rates in glaucoma surgery these days.²²

Pflugfelder: Glaucoma is probably the biggest risk factor for the failure of corneal transplants. Boisjoly et al conducted a study and showed that it was really glaucoma drops that were a big risk for failure or rejection.²³

CASES

No. 1

Lin: An 87-year-old male presented with moderate-to-advanced glaucoma. His IOPs were relatively controlled on timolol 0.5% OU b.i.d. Specifically, the pressures were 14 mm Hg OD and 17 mm Hg OS, and his eyes were of normal corneal thickness. The cup-to-disc ratios were 0.9 OD and 0.8 OS. There was significant visual field loss, especially in the patient's right eye (Figure 1). Progression from the prior visual field was evident.

My target IOPs for this patient were the low teens. I wanted to add a prostaglandin to his drug regimen to further lower his pressure. I added the new formulation of travoprost OU q.h.s. I warned him about possible ocular redness and other potential side effects.

The patient returned 1.5 months later (Figure 2). He does not have Grave's disease,

and my request that he open his eyes wide probably accounts for their exophthalmic appearance. At the follow-up visit, the patient's eyes were not significantly red. He did not complain of any changes in his symptomatology or of ocular redness, irritation, or discomfort. His IOPs had decreased to 10 mm Hg OD and 14 mm Hg OS.

Kahook: Would you consider discontinuing the timolol?

Lin: It is something I have been considering. At his 3-month follow-up, the patient was still doing well. I may notice a bump in his IOP when I am seeing

him during the day, but beta blockers do not have a significant effect during the nocturnal period.^{3,4} I may discontinue the timolol at the next visit if his pressure stays low.

Gross: I think you are right first to confirm the efficacy and to make sure his pressure is well controlled. A nice way to stop the timolol might be a reverse one-eye trial. The difference in IOP between the patient's two eyes is fairly consistent. Stopping the drug in only one eye—maybe his left eye, which has the more normal field—might permit you to quantitate the timolol's efficacy.

Kahook: You might also proceed in a stepwise fashion. Perhaps instruct the patient to use the timolol q.a.m. only.

Pflugfelder: Regarding the appearance of the patient's eyes, he may have a little bit of lid retraction. Maybe his blink rate is down, which would mean the drug is not clearing out of his eye. Many elderly patients do not blink well if they have Parkinson's disease or are on medications, and this is a setup for preservative-related toxicity.

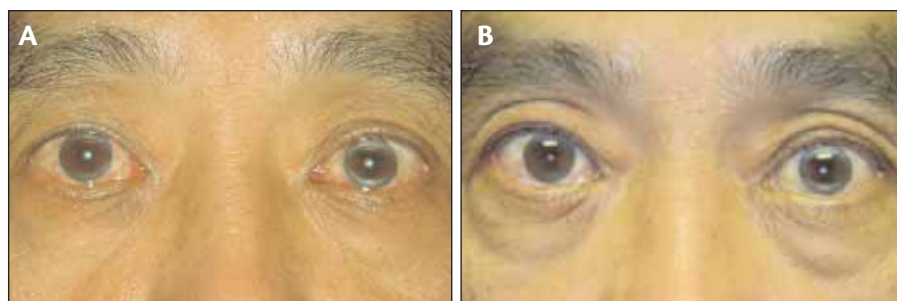


Figure 4. The patient described in Case No. 2 had red eyes while using the original formulation of travoprost (A). They improved after his switch to the new formulation of travoprost (B).

(Courtesy of Ronald Gross, MD.)

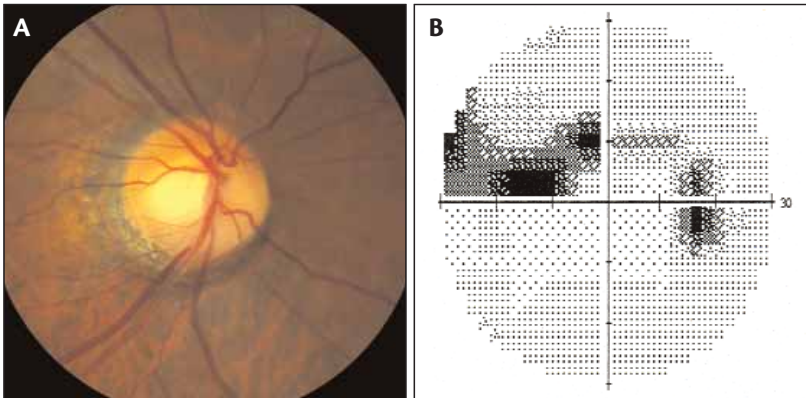


Figure 5. In Case No. 4, this optic disc photograph demonstrated a substantial loss of the neuroretinal rim in the patient's right eye (A), and there was a corresponding, typical, nerve fiber layer distribution of the visual field involving the superior arcuate distribution and nasal step (B).

No. 2

Lin: This 59-year-old male was diagnosed with POAG. His IOPs were 15 mm Hg OD and 13 mm Hg OS, and he had normal corneal thicknesses of 550 μ m OD and 560 μ m OS. Both eyes had a cup-to-disc ratio of 0.7.

The patient had been using the original formulation of travoprost for approximately 1 year, and he complained of mild redness of his eyes. He also frankly told me that he would sometimes miss a dose due to the redness and irritation he was experiencing. He had lost some peripheral vision in both eyes (Figure 3).

I switched the patient to the new formulation of travoprost. Four to 6 weeks later, improvement was visible in both eyes (Figure 4). The prominent pinguecula may highlight the injection. The patient's adherence to prescribed therapy improved, and his IOPs decreased to 12 mm Hg OD and 12 mm Hg OS. He told me that his eyes were less red and more comfortable.

No. 3

Gross: A 20-year-old female had aniridia and had been using latanoprost ophthalmic solution (Xalatan; Pfizer, Inc., New York, NY) for 5 years. Her pressures were in the high teens. She had recently undergone cataract surgery, and her comprehensive ophthalmologist had discontinued the prostaglandin due to concern about her ocular surface. The patient's nystagmus and pupillary size made it dif-

ficult for me to assess her optic nerves. By history, her comprehensive ophthalmologist noted that the patient's optic nerves were healthy but that her pressure was between 22 and 24 mm Hg.

Steve's and my concerns about the patient's aniridia and potential problems with corneal pannus prompted us to prescribe the new formulation of travoprost. Her IOP decreased to approximately 15 mm Hg OU.

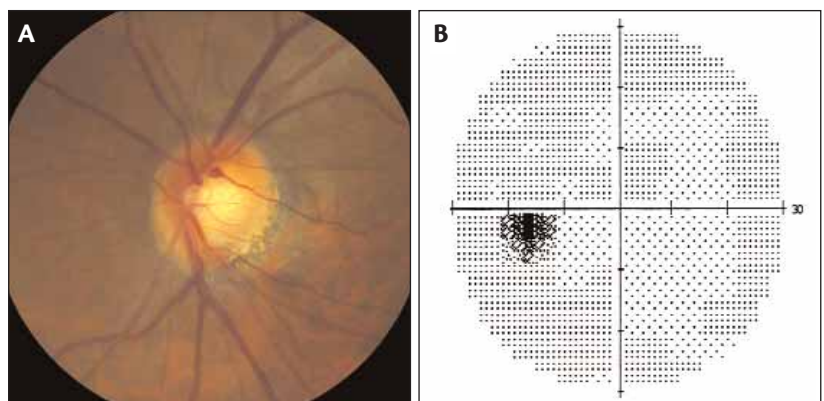
Pflugfelder: This is definitely a patient in whom you want to avoid BAK. In their teens or 20s, almost all patients with aniridia develop either a mild or severe stem-cell deficiency,

and we do not want to accelerate that process. They almost all have glaucoma, just like this patient. I think the new formulation of travoprost is an excellent option for a patient such as this one.

No. 4

Gross: A 68-year-old patient presented with well-controlled IOPs on latanoprost and a fixed combination of timolol and dorzolamide (Cosopt; Merck & Co., Inc.). He used artificial tears q.d. and had moderate disease (Figure 5).

Kahook: If he lives long enough, this patient may require trabeculectomy surgery. I would therefore be inclined to discontinue the latanoprost with 0.02% BAK in favor of the new formulation of travoprost. IOP-lowering efficacy among the prostaglandin analogs is essentially equal, and



(Courtesy of Ronald Gross, MD.)

Figure 6. In Case No. 5, this optic disc photograph showed very early glaucomatous damage with a mild loss of the inferior neuroretinal rim (A), and there was a minimal, demonstrable defect on standard automated perimetry (B).

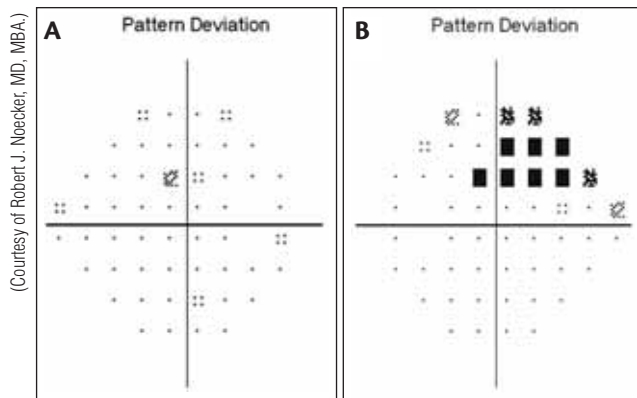


Figure 7. The patient described in Case No. 8 had a normal visual field in his right eye (A), but testing revealed a superior nasal step in his left eye (B).

the switch is not likely to cause a disruption in IOP control.²⁴ Doing so may increase the potential for successful future surgery by decreasing chronic conjunctival inflammation and the proliferation of fibroblasts.

No. 5

Gross: A 55-year-old with rheumatoid arthritis presented with substantial signs and symptoms of ocular surface disease. She was newly diagnosed with POAG. Her visual field looked pretty good, but there was some thinning of the inferior rim of the optic nerve in her left eye (Figure 6). Clearly, the patient should begin therapy for glaucoma, and prescribing a medication containing BAK could exacerbate her existing problems.

Pflugfelder: A confounding factor in patients such as this one can be corneal thinning, which is another reason to keep the corneal surface as healthy as possible. Epitheliopathy is only going to trigger more proteases and further thinning.

Noecker: I think that this is a case in which using a BAK-free glaucoma medication as first-line therapy should certainly be considered.

Lin: This approach will save her decades of exposure to BAK.

No. 6

Gross: A 60-year-old male presented with mild POAG, well-controlled pressures on latanoprost, and substantial corneal staining. I switched the patient to the new formulation of travoprost. Four weeks later, the patient still

had essentially no symptoms. My assumption was that he might develop the symptoms later and that eliminating the BAK would minimize the risk.

Noecker: The long-term gain is there. Not every eye is going to look perfectly white.

No. 7

Pflugfelder: An 86-year-old male presented with complaints of tearing, severe redness, and discharge in his right eye for 1 month. He had a history of complicated cataract surgery and glaucoma in his right eye and had been using brimonidine tartrate in that eye only for 2 years. His IOP was 15 mm Hg OD. I noted marked punctal ectropion, conjunctival injection, and papillary reaction on the inferior tarsal conjunctiva. I suspected a toxic or allergic conjunctivitis due to the brimonidine, so I stopped that agent and prescribed the new formulation of travoprost.

One month later, the patient's complaints had resolved. There was no conjunctivitis, and his IOP was 12 mm Hg. His punctal ectropion had increased the likelihood of his developing a toxic allergic reaction, because the eye was not draining properly.

Lin: Would you say he had an allergy to the brimonidine?

Pflugfelder: That is what it looked like to me.

Gross: In this case, the patient was already taking a BAK-free medication, but the agent was the offender. You have an option to switch the drug without adding BAK.

No. 8

Noecker: A 38-year-old male presented with a complaint that his tolerance for contact lenses had decreased. The patient had been taking latanoprost for several years and was using some artificial tears. Before therapy, his IOPs were 26 mm Hg OU, and, currently, they were 17 mm Hg OU. His optic nerves had thinning inferiorly, and visual field testing confirmed a nasal step in his left eye (Figure 7). The patient exhibited typical pigmentary changes. The tear breakup time was less than 5 seconds.

The patient expressed a desire to continue wearing contact lenses, so we discussed stopping the latanoprost. We decided to have him try the new formulation of travoprost. Six weeks later, he could wear his contact lenses longer. His tear breakup time was nearly 10 seconds, and his IOP measured 16 mm Hg.

(Courtesy of Malik Y. Kahook, MD.)

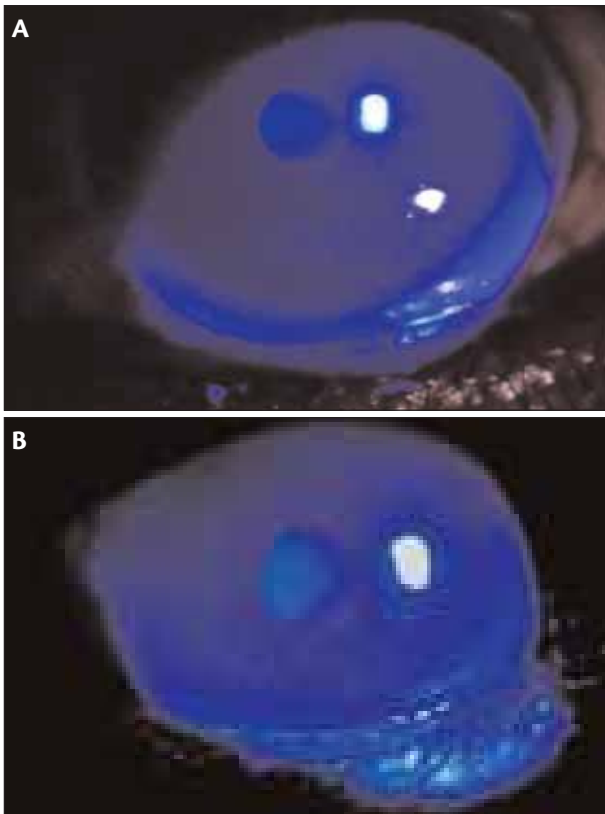


Figure 8. At the slit lamp, fluorescein staining of the cornea of the patient described in Case No. 9 revealed punctate epithelial erosions that were more noticeable inferiorly (A). After the patient switched from latanoprost to the new formulation of travoprost, fluorescein staining of the punctate epithelial erosions decreased (B).

Pflugfelder: The patient's contact lenses may have been a risk factor for an adverse reaction to the medication. If it is soaked up by the contact lenses, the BAK is in direct contact with the cornea longer.

No. 9

Kahook: A 73-year-old female presented with a complaint of ocular irritation. Her POAG had been treated for 8 years with latanoprost q.d. OU, and her pressures were 11 mm Hg OU. She had dry eyes, for which she had been treated with artificial tears, a mild steroid, and punctal plugs.

On testing, she exhibited extensive fluorescein pickup, especially inferiorly on her cornea (Figure 8). I switched the patient to the new formulation of travoprost, and her ocular surface improved. Her IOPs remained stable at 11 to 12 mm Hg OU. A few areas of fluorescein pickup

are evident on the right side of the cornea after the patient's switch to the new formulation of travoprost, but an improvement in clinical signs was unmistakable. Perhaps more importantly, she subjectively noted greater comfort and a decrease in her symptoms of dry eye. ■

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CME QUESTIONS

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1. Which of the following classes of glaucoma drugs is used most frequently as first-line therapy in the US?
 - a. Beta blockers
 - b. Carbonic anhydrase inhibitors
 - c. Alpha agonists
 - d. Prostaglandin analogs
2. Which of the following statements is false?
 - a. BAK is an ineffective preservative system
 - b. BAK can disrupt the corneal-barrier function
 - c. BAK increases the penetration of a drug
 - d. BAK increases the levels of inflammatory cytokines in the tear film and the levels of inflammatory cells in the conjunctival epithelium and stroma
3. Currently available ophthalmic medications preserved with BAK contain the same concentration of this agent.
 - a. True
 - b. False
4. Preexisting dry eye disease can make a patient more vulnerable to harm from BAK-preserved medications.
 - a. True
 - b. False
5. Which of the following is not an indicator of potential ocular surface disease?
 - a. The patient complains of ocular burning or redness
 - b. The patient describes fluctuations or a decrease in visual acuity
 - c. The patient's eyes show evidence of corneal epithelial staining after the instillation of fluorescein
 - d. The patient does not use artificial tears
6. Punctal occlusion may worsen preservative-related toxicity.
 - a. True
 - b. False
7. Studies have demonstrated that glaucoma medications containing BAK lower IOP more effectively than those without BAK.
 - a. True
 - b. False
8. Switching patients from a glaucoma medication preserved with BAK to one with an alternative preservative system is likely to produce an improvement in their ocular surface in 1 week.
 - a. True
 - b. False
9. The options recommended by the panelists for treating patients with concurrent glaucoma and ocular surface disease were:
 - a. Switching from a glaucoma medication containing BAK to one without this preservative
 - b. Prescribing BAK-free artificial tears
 - c. Prescribing anti-inflammatory therapy such as topical cyclosporine
 - d. Prescribing oral tetracycline
 - e. A and B
 - f. All of the above
10. Contact lens wear can prolong the contact between a topical medication and the eye.
 - a. True
 - b. False

