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CURRENT APPROACHES ...
NEW POSSIBILITIES

The Management of Glaucoma and Ocular Hypertension

HIGHLIGHTS FROM A ROUNDTABLE DISCUSSION HELD IN JANUARY 2008

Featuring:

L. Jay Katz, MD, Moderator
Jorge A. Alvarado, MD
Robert J. Noecker, MD, MBA
Thomas W. Samuelson, MD

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Current Approaches ... New Possibilities

The Management of Glaucoma and Ocular Hypertension

A ROUNDTABLE DISCUSSION

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STATEMENT OF NEED

In the last decade, numerous novel ocular hypotensive agents have been introduced for the control of IOP. When selecting an ocular hypotensive medication for their patients, clinicians should consider not only its IOP-lowering ability, but other factors that will affect efficacy, tolerability and patient adherence, such as the dosing schedule and the preservative used.

TARGET AUDIENCE

This activity is designed for ophthalmologists.

LEARNING OBJECTIVES

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

- Discuss the various components of therapeutic eye drops for glaucoma.
- Identify the effects of preservatives on efficacy and tolerability of glaucoma drops.
- Describe the decision-making process for choosing a glaucoma therapy, including when to add or switch therapies.
- List current therapeutic options, including fixed combinations, and their role in glaucoma management.

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. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you experience problems with the online test, please email us at support@dulaneyfoundation.org and explain the details of any problems you encounter with the Web site. You also may fax your exam to us at (610) 771-4443. Please note, if you fax your test, you must include your full name and an email address, as certificates are issued electronically.

Upon completing the activity and achieving a passing score of 70% or higher on the self-assessment test, participants may print a CME credit letter awarding 1.5 *AMA PRA Category 1 Credits.*™ The estimated time to complete this activity is 1.5 hours.

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FACULTY DISCLOSURE DECLARATIONS

L. Jay Katz, MD, (Moderator) has received grant/research support from Allergan, Inc., Alcon Laboratories, Inc., Lumenis, Ltd., and Pfizer, Inc. He is on the speakers bureaus of Allergan, Inc., Alcon Laboratories, Inc., Ista Pharmaceuticals, Lumenis, Ltd., Merck & Co., Inc., and Pfizer, Inc.

Jorge A. Alvarado, 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., Endo Optiks, and Lumenis, Inc.

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Additional staff who assisted with planning, editing and peer review of this supplement state that they have nothing to disclose.

FACULTY CREDENTIALS

L. Jay Katz, MD, is Director of the Glaucoma Service at Wills Eye Institute and Professor at Jefferson Medical College. Dr. Katz may be reached at (215) 928-3197; ljk22222@aol.com.

Jorge A. Alvarado, MD, is Professor of Ophthalmology at the University of California, San Francisco. Dr. Alvarado may be reached at (415) 476-3944; alvaradoj@vision.ucsf.edu.

Robert J. Noecker, MD, MBA, is Director of the Glaucoma Service and Associate Professor/Vice Chair at the Department of Ophthalmology at the University of Pittsburgh. Dr. Noecker may be reached at (412) 647-2152; noeckerrj@upmc.edu.

Thomas W. Samuelson, MD, is Adjunct Associate Professor at the University of Minnesota in Minneapolis and Attending Surgeon at Minnesota Eye Consultants/Phillips Eye Institute in Minneapolis. Dr. Samuelson may be reached at (612) 813-3628; twsamuelson@mneye.com.

The Making of Glaucoma Drops

What are the clinical implications of ophthalmic drug formulation? Lowering IOP is the goal for glaucoma medications, but other factors will influence efficacy.

Katz: Our discussion focuses on topical formulations for treating glaucoma: how they are developed; and the factors that affect their efficacy and tolerability. We also will discuss the role of preservatives and the feasibility of altering or replacing them to minimize their adverse effects on the eye.

Let's begin by discussing the process of making an eye drop that delivers drug effectively for treating glaucoma.

FORMULATION COMPLEXITIES

Noecker: Formulating an eye drop is a relatively complex process. Each formulation has multiple components: the active ingredient; the vehicle; and other compounds that enhance the vehicle. First, you must determine if the compound is soluble in an aqueous formulation. In addition, the pH must be physiologic when delivered to the eye, and the drug must be stable. Normal solutes must be biocompatible with the tear film and the ocular surface. Finally, the drop must be therapeutic.

Katz: Dr. Alvarado, what can you tell us about bioavailability in the anterior chambers of animal eyes?

Alvarado: The concentration of a therapeutic agent in an eye drop decreases progressively as it passes through the layers of the eye into the target tissue in the anterior chamber. Therefore, to deliver the agent inside the eye at its most effective level, the active ingredient must be formulated at a much higher concentration.

For example, ethacrynic acid induces an effect on aqueous outflow at micromolar concentrations (ie, ~10^{-6} M). This implies that for ethacrynic acid to work as a topically applied medication, it must be formulated at a much higher concentration (ie, ~100 to 1000 times higher or 10^{-3} M). If applied topically at such a high concentration, ethacrynic acid might become toxic and intolerable to patients. Studies of ethacrynic acid have been performed in monkeys and other laboratory animals, as well as in target cells cultured from the human outflow pathway.[1]

"The concentration of a therapeutic agent in an eye drop decreases progressively as it passes ... into the target tissue."
—Jorge A. Alvarado, MD

Katz: People talk about avoiding problems with surface toxicity and maybe even systemic toxicity by using prodrugs. Do we have any prodrugs for glaucoma?

Samuelson: The classic prodrug is dipivefrin (Propine; Allergan, Inc., Irvine, CA), which helps avoid some epinephrine-related systemic side effects as it is converted to a clinically active form while crossing the corneal tissues. The prodrug concept is a useful one as it will reduce the amount of active drug that is absorbed systemically. For example, spillover drug enters the body in an inactive form through the nasolacrimal system.

It is difficult to find the perfect eye medication that will ensure maximal compliance. An eye drop must be comfortable. It must have ingredients that will prevent contamination, it must have a favorable safety profile, few adverse effects, and, of course, it must be efficacious. To produce such a medication is a tall order. The prodrug is a good concept and makes drugs safer and better tolerated, but it is not always easy to achieve all of the criteria that define a successful medication.

PRESERVATIVE PROS AND CONS

Katz: Let's discuss the introduction of preservatives in ophthalmic preparations. What are the concerns?

Noecker: The FDA recognized the potential for contamination in the 1950s when almost all ophthalmic

preparations were made by compounding pharmacies. At that time, the FDA mandated that all ophthalmic preparations in multi-use vials be preserved.

Katz: What are the regulatory agencies looking for in preservatives?

Noecker: The primary role of preservatives is to stop the growth of organisms, although preservatives also play a part in stability and drug penetration. Specifically, the FDA looks at the ability to kill common organisms, such as *Pseudomonas*, with exposure over time.

Katz: Some compounding organizations will make preservative-free preparations of commonly used drugs. How do you feel about that?

Noecker: We certainly can have preservative-free ophthalmic preparations made, but I worry about doing this with glaucoma medications. You cannot control the human factor or the post-production

ACTIVE INGREDIENT'S VERSUS PRESERVATIVE'S EFFECT ON SURFACE TOLERABILITY

Katz: Both the active ingredient and the preservative in a glaucoma drop may have an effect on surface tolerability. Studies by Baudouin and others note changes in cell type (eg, inflammatory cells) that are dose dependent on the amount and duration of BAK load.[1] Dr. Alvarado, is there a dose response curve with benzalkonium chloride (BAK) in terms of affecting the surface of the human eye?

Alvarado: BAK has definite and pronounced cellular effects when it comes in contact with a wide variety of cell types. Weinreb and I studied the ultra structural effects in corneal endothelial cells after subconjunctival injections containing BAK.[2] BAK is remarkably toxic to the corneal endothelial cells, inducing extensive vacuole formation. I would expect that the epithelial surface would undergo similar changes upon chronic exposure to BAK, but I suspect that the cell density of the epithelial surface would likely remain unchanged.

Regarding a BAK dose-related response in terms of patient tolerability, Dr. Samuelson has pointed out that although bimatoprost has only 0.005% BAK compared to latanoprost having 0.02%, "clearly latanoprost is well tolerated on the ocular surface for most patients" despite having a higher BAK concentration. So as Dr. Katz said at the outset, the relationship is not one that is simply related to the BAK concentration (or "dose"), but to an interaction between the active ingredient and the preservative. I also have the same impression as Dr. Samuelson does, that for unknown reasons the clinical problem of hyperemia and toxicity appear to have abated recently.

Katz: With a fixed combination of brimonidine/timolol, there is a lower rate of allergic reactions compared with brimonidine used alone. A proposed explanation is based on the model of adrenergic regulation of cell volume. Can you explain this hypothesis and the previous work that supports this concept?

Alvarado: Two reports discuss several pertinent issues regarding the relationship between cell volume effects and specific adrenergic receptors.

One article describes the puzzling propensity of certain BAK-containing adrenergic agents to induce untoward reactions. While this study focused on the alpha-2 agonist apraclonidine hydrochloride (Iopidine), it was also concerned with epinephrine and dipivefrin, which have alpha- as well as beta-receptor activity. We also considered that the ocular surface cells interact with relatively high concentrations of adrenergic agents, which might induce some beta-receptor activity even in adrenergic agents that are relatively specific for alpha receptors.[3]

The second article discusses the ability of particular beta-adrenergic agonists to induce cell-shrinkage and how such an effect may promote interaction between toxic agents on the conjunctival surface with stromal tissues in the subepithelial space.[4]

Using data from both articles, we can postulate a mechanism whereby an adrenergic agent might induce untoward effects more frequently than other types of glaucoma medications. As mentioned earlier, the concentration of these agents when interacting with the ocular surface is much higher than that reaching tissues inside the eye. At such high concentrations, the existence of some beta-receptor activity may become apparent as shrinkage of epithelial cells lining the ocular surface. The net result would be widening the intercellular space, which would provide greater access to underlying subepithelial tissues than otherwise possible.

Thus, BAK, altered tear-film lipids, and other pro-inflammatory agents can reach and interact with vascular and other subepithelial tissues, inducing hyperemia and chronic inflammatory changes similar to those well-

storage conditions. Also, the rules governing compounding pharmacies are vague. A facility can be involved in other activities and still be a compounding pharmacy. Whereas a manufacturing plant is held to rigorous standards mandated by the FDA.

Katz: Aside from concern about infection, what about the efficacy of a nonpreserved preparation? No one is checking the efficacy of that preparation.

Noecker: That is a good point, especially for glaucoma medicines. It is not a trivial task to ensure sufficient penetration through the ocular surface at concentrations capable of achieving a therapeutic effect.

Samuelson: Safety is my first concern. We can judge if a drug is reducing pressure, but we have a lot less control when assessing safety. If a patient comes in with a problem—a corneal ulcer, for example—it is impossible to turn back the clock. For efficacy, at least we can try a different approach if a drug is not working.

described histological alterations in the subconjunctival tissues of glaucoma patients.[5] The net effect might be drug intolerance due to specific ocular surface effects induced by high drug concentration and some beta-receptor activity apparent under conditions where a BAK-containing adrenergic agent is used.

Katz: So how do you block the cell shrinkage process?

Alvarado: We showed that the cell volume effect was mediated by beta-receptor activity, as it could be blocked 100% with pretreatment with the nonspecific beta-blocker timolol maleate. This suggested that perhaps one way to lessen the incidence of untoward adrenergic agonist reactions—mediated by opening the paracellular pathway—might be to treat patients concurrently with a beta-blocker. Others have pointed out recently that there might be other beneficial effects associated with the use of timolol, including antioxidant effects.[6]

A word of caution is warranted at this point. As discussed extensively in our second article, it is hazardous to predict the effect of a specific adrenergic agent from the experience in one tissue to that in another.

Finally, we would like to point out that prostaglandins also induce a change in cell size, as demonstrated by Neufeld more than two decades ago.[7] Thus, prostaglandin analogs also may benefit from the concurrent use of beta-blockers in a combined formulation. In fact, the early European experience with a prostaglandin analog/timolol combination shows that patient tolerability may be enhanced.

My interest in this area from a clinical point of view was revived most recently by the introduction of the brimonidine/timolol combination known as Combigan (Allergan, Inc., Irvine, CA). It never occurred to us that adding timolol to the adrenergic agonist brimonidine would increase tolerability compared to the situation when brimonidine is applied alone.

Samuelson: With your hypothesis, would you speculate that patients who had been taking beta-blockers prior to an alpha-2 adrenergic had better tolerability than those who were not?

Alvarado: This is a complex question, which deals with the issue of tolerability. Tolerability involves untoward effects due to general effects such as hyperemia and nonspecific chronic inflammation as well as allergy-mediated responses. In the Osborne study, the authors comment that: "… Timoptol used prior to Alphagan seems to confer some protection against Alphagan allergy."

Samuelson: But that does not necessarily mean that patients who are on beta-blockers prior to initiating alpha-2 agonists experienced the same preventive effect.

Alvarado: Clinically, I never thought that would be the case, but it might be so, and soon we shall learn what the facts are, as this has become a clinically relevant question.

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Katz: Yes. We cannot compare the situation to a 1-week course of topical steroids, for example. In glaucoma, the concern is that a patient is using a product for an extended period—maybe a month or longer—and we know that contamination is a possibility, even with a preservative. Contamination is clearly higher in bottles without preservatives. One study found that 10% of preservative-free, multi-dose bottles were definitely contaminated with pathogens.[2] I have always been concerned about using a drop on a repeated basis for an extended period, particularly in eyes of elderly patients whose immune systems and epitheliums are already compromised.

TYPES OF PRESERVATIVES

Katz: Let's discuss the specific preservatives used.

Noecker: Most glaucoma medicines are preserved with benzalkonium chloride (BAK). A fairly low concentration of BAK achieves the USP standards for kill curves for organisms. I believe that is why it is used so extensively.

The amount of BAK varies in the different glaucoma preparations. One reason for that is historical. Timolol maleate, introduced in 1978 as Timoptic (Merck & Co. Inc., Whitehouse, NJ), is almost always preserved with 0.01% BAK. It became the gold standard drug, and I do not think there was ever push for a nonpreserved version.

Some newer medications have about half the amount of BAK as timolol. For example, bimatoprost (Lumigan; Allergan Inc., Irvine, CA) has 0.005% BAK, which seems to be the lower limit that easily achieves the necessary kill curves. At the other extreme is latanoprost (Xalatan; Pfizer, Inc., New York, NY) with 0.02% BAK. The preservative concentration is this high, not so much because latanoprost is more likely to grow bacteria in the bottle, but because it is an unstable molecule. As such, it needs the higher amount of BAK for its detergent-like properties that help stabilize the more complex molecule.

One reason why we do not eliminate BAK from ophthalmic preparations is because it would be an expensive and time-consuming process. Another reason is because all molecules are not compatible with some of the newer preservatives.

Katz: Dr. Noecker, you have done some work with Purite, the preservative in brimonidine (Alphagan-P; Allergan, Inc., Irvine, CA). Will you elaborate on it?

Noecker: Purite is a stabilized oxychloride compound. It was originally introduced in the artificial tear market, so we are familiar with it. Once exposed to sunlight, Purite breaks down very quickly, and the relative toxic components disappear. It is an oxidizing compound, so it is selective. It is more toxic to bacteria than it is to mammals, because mammals can have an infinite supply of antioxidants as compared to bacteria.

Katz: Sofzia, the preservative in the newest formulation of travoprost (Travatan Z; Alcon Laboratories, Inc., Fort Worth, TX), is a combination of several different components.

Noecker: Sofzia is a combination of borate, sorbitol, polyols and zinc in a proprietary mixture. It appears to be relatively effective in terms of killing bacteria that are relevant to ophthalmology.[3,4] The physiology is probably less well understood, but it appears that this mixture is capable of disrupting several different metabolic processes of bacteria while not causing significant harm to mammalian epithelial cells at the concentrations used in these eye drops.

Katz: Dr. Noecker mentioned there are different BAK concentrations in some of the glaucoma preparations. Is that important? Is there some dose response in terms of surface toxicity with BAK?

Samuelson: In my experience, a very vocal minority of patients have issues with BAK. However, in a consultative practice, I tend to see a lot of those who struggle with preservative toxicity, so I like having alternatives for those patients.

One point I typically make is that bimatoprost has 0.005% BAK and latanoprost has 0.02%, or four times more BAK, but if you look at population studies of hyperemia and surface complaints with the two agents, latanoprost is well tolerated on the ocular surface for most patients.[5,6] So some patients are reacting to the active compound not the preservative. Clearly, both may be factors, so it is good if you can keep the BAK low. Bimatoprost has a very low BAK concentration, travoprost now has a BAK-free option, and I think it is a big advance for alpha-2 agonists to be able to have a BAK-free brimonidine preparation. ■

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Exploring Ocular Surface Sensitivity in Glaucoma Therapy

When patients present with corneal complaints or signs of irritation, what is to blame, and how can it be addressed?

Katz: What causes surface sensitivity with the use of various glaucoma products? Are the reactions caused by allergy or toxicity?

Noecker: That is a relatively complex question, and the answer differs with each drug. You have to consider the active ingredient and how it behaves therapeutically, as well as any other effects it will have on the ocular surface. The preservative also can be involved. Certainly, when we use agents that contain detergent preservatives, the amount and duration of exposure can affect the ocular surface.

Another factor is the pH; pH disturbances can greatly alter the surface and disrupt the natural tear film. Other components, such as lubricating and viscosity agents, can be involved.

With the alpha agonists, the active molecule is probably most responsible for allergy. Studies of brimonidine show oxidation of the active drug is responsible for the allergy, so the issue tends to be concentration-dependent.[1]

Most importantly, the oxidation potential of each drug appears to have nothing to do with the mechanism of action, but alpha agonists may allow the oxidized compound to penetrate the ocular surface.

In terms of mechanism of action, the carbonic anhydrase inhibitors (CAIs) can affect the endothelial cell pump function. A patient with a compromised cornea may develop some corneal edema, which will change the ocular surface and lead to problems. The periocular changes we often see are due to toxicity more than allergy.

With the prostaglandin analogs, in the short term, hyperemia probably is due to the drug and how it interacts with receptors on blood vessels.

Timolol is well tolerated because the drug itself does not seem to adversely affect the ocular surface.

"Hyperemia associated with the prostaglandin analogs seems to be due to the action of the drug on the vessels and tends to be short term."
—Robert J. Noecker, MD, MBA

DIFFERENTIATING HYPEREMIA

Katz: Is the hyperemia that you get with brimonidine the same as what you see with a prostaglandin?

Noecker: Hyperemia associated with the prostaglandin analogs seems to be due to the action of the drug on the vessels and tends to be short term. It is at its worst after the initial dose, and then it tends to diminish over time, typically 2 weeks. In clinical practice, however, you may see some longer term hyperemia, which is more of a multifactorial issue.

In contrast, hyperemia associated with the alpha-2 agonist allergy does not appear with the first dose but develops over time in individuals who are susceptible. The effect may be cumulative, owing to alterations in the ocular surface, allowing the oxidized compound to penetrate.

MEIBOMIAN GLAND AND TEAR FILM CHANGES

Alvarado: At our clinic, I have noticed that meibomian gland dysfunction is far more prevalent in glaucoma patients than in non-glaucoma patients. For this reason, I wonder if a meibomian gland effect is related to the preservative, the active ingredient, and the combination of both. Also, does the lipid profile on the ocular surface

change with a preference disequilibrium to the more toxic profile of agents?

Noecker: Looking at chronic exposure with some of the older glaucoma medications, we see a decrease in functional goblet cells, and the mucin they excrete changes with time.[2,3] It may be simpler to look at tear film composition. Often, the type of lipids changes, and the lipid layer decreases. Some evidence exists that more pro-inflammatory types of lipids may be present.[4]

Katz: Do you feel tear breakup time changes with the use of glaucoma products, particularly those with BAK?

Noecker: Tear breakup time changes with almost everything you put in the eye. You need almost perfect equilibrium between the lipid layer, the aqueous layer, and the mucin layer. Skewing any one of them—with a detergent preservative, for example—will disrupt the surface.

"The hyperemia associated with bimatoprost ... is more of a vasodilatory response without the inflammation."
—Thomas W. Samuelson, MD

Katz: As glaucoma specialists, we are not really attuned to evaluating the tear film and the ocular surface. I am impressed by its complexity and how there is sometimes a disconnect between signs and the symptomatology that patients express. Some studies in France have looked at beta-blockers with and without BAK. They found the introduction of BAK definitely affects tear breakup time beyond what the drug may do.[5]

Alvarado: You are referring to lacrimal gland dysfunction, which is a beta-blockade effect in addition to the events that we are discussing. My understanding has been that a dry eye with beta-blockers is related to an alteration in tear secretion by the lacrimal gland and the accessory glands. What is overwhelming is the complexity of the issues, not only the therapeutic effect of the drugs, but also their effects on the ocular surface.

Katz: Have studies using impression cytology, conjunctival biopsies and the like shown anything conclusive?

Samuelson: Are there differences between some of the surface irritant responses we see? Personally, I think definitely there are. Broadway's study of patients pre- and post-glaucoma medications at the time of surgery clearly showed inflammatory cells and monocyte migration and activation.[6] You do not see that with the hyperemia associated with bimatoprost, for example, which is more of a vasodilatory response without the inflammation. So for many patients, there is a significant difference. One is more of a toxic inflammatory response, and the other is more of a vaso-active response, the latter being the preferred of the two.

ARTIFICIAL TEARS VERSUS GLAUCOMA DROPS

Katz: Dr. Noecker, you mentioned that some glaucoma products are high in BAK. Do you know what concentrations are in artificial tear preparations?

Noecker: None of the mainstream, newer branded artificial tears contains BAK. However, in the general marketplace, many older preparations or generic formulations do contain it. I do not know what percentage of the market is generic artificial tears, so I cannot quantitate it.

Katz: Do you think the artificial tear manufacturers are ahead of the curve, meaning that they are ramping up to be nonpreserved or non-BAK preserved?

Noecker: Yes, definitely. Dry eye and ocular surface disease are complex multifactorial conditions. It is difficult to show differences in improvement with any of the therapeutic interventions, much less assess patients' complaints consistently. Frequently, with many ocular surface disease patients, there is no correlation between signs and symptoms. You may see a patient who has severe rosacea, for example, but he is not the patient who is complaining. Even dry eye researchers have had problems reaching therapeutic endpoints.

Our next step is to tailor our glaucoma therapy strategy around this. That is another step of complexity. This is something we need to think about. But to show a cause and effect is difficult at that level. ■

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How Preservatives Affect Efficacy and Tolerability

The panel considers the latest glaucoma formulations with non-BAK preservatives and discusses concerns with generic drops.

Katz: When BAK was first developed, one of the pluses was that it caused some changes in the corneal epithelium and perhaps allowed for better drug penetration and improved drug bioavailability internally. That could be potentially very important for glaucoma products. What is your opinion of the current glaucoma products that may not have BAK? Was efficacy decreased?

Noecker: About 5 or 6 years ago, brimonidine with Purite (Alphagan-P; Allergan, Inc., Irvine, CA) was introduced. Some initial studies showed that changing the preservative and some other components, and increasing the pH may have enhanced penetration of the brimonidine molecule into the anterior chamber. I think that is evidence that BAK probably is not essential for efficacy.[1]

Similarly, there appears to be no difference in efficacy between travoprost with BAK and travoprost with Sofzia.[2] Studies of preservative-free preparations in Europe suggest no difference in efficacy.[3] I think it really depends on the molecule. Sometimes, changing the ocular surface is beneficial for some molecules, and other times, it is probably less so.

For glaucoma medications, the preservative is largely a neutral factor in terms of penetration and therapeutic efficacy when we look at IOP lowering.

Samuelson: The alpha-2 agonists illustrate some of the points we have been discussing. In that class, we started with apraclonidine, which had a profound pressure-lowering effect at 2 hours. Then came brimonidine, an agent that is much more alpha-2 selective. It minimized a lot of the side effects, which was an obvious improvement, but the 0.2% formulation caused significant surface issues and allergy.

Then Purite was developed. The brimonidine concentration was reduced to 0.15%, and later 0.1%, and bioavailability improved with the formulation changes. So with less drug and a BAK-free vehicle, we saw substantial improvements.[4]

So that class and its evolution demonstrates what we are talking about today: improved tolerability while maintaining efficacy.

GENERIC CONCERNS

Alvarado: Dr. Noecker, you commented that generic drugs have not switched from BAK to some of the other preservatives. Is that a concern in terms of efficacy of the generic counterpart?

"For glaucoma medications, the preservative is largely a neutral factor in terms of penetration and therapeutic efficacy when we look at IOP lowering."
—Robert J. Noecker, MD, MBA

Noecker: It is a potential source of variability, especially when you consider that generic preparations do not have to go through clinical trials. They must merely show bioequivalence in the labeling. But what looks good on paper sometimes is not. If just one small component is different, the effect may not be exactly the same. We see that in generic brimonidine. We have become accustomed to the good tolerability of the branded brimonidine family. However, in my experience, if I must switch a patient to the generic formulation for formulary reasons, it is not as well tolerated.

Katz: The regulation of generic products is different from what is required of a branded product, specifically the type and concentration of preservative that is used. Does anyone recall the story about Voltaren and generic diclofenac?

Samuelson: I did not have a lot of direct experience

with it, but most ophthalmologists know the story. The generic diclofenac caused corneal issues, especially when used chronically.[5] Although we did not see that with branded Voltaren, the product was taken off the market.

Katz: That is amazing, though, because the alteration was subtle. Even though it was the same active ingredient, there definitely was a difference between the branded product and the generic product.

Nothing that glaring has happened in the ophthalmic market since then, but I know that generic brimonidine has not been embraced. I think a lot of that has to do with the perception of how it works and how patients tolerate it, even though it is the same drug. Timolol, on the other hand, has become generic very quickly.

Noecker: The other lesson from the generic diclofenac story is that for a number of years, a lot of people stopped—or did not start—using topical NSAIDs because they thought it was a class effect. It was simply a formulation effect, which I think surprised many people.

EFFICACY, SAFETY, COMFORT

Katz: When discussing glaucoma products—and we have talked about the different preservatives and formulations—what is the most important factor?

Noecker: It is all about efficacy. When patients are referred to me, the directive is, "Lower this patient's intraocular pressure," either therapeutically or surgically. That is our role. In an ideal world, where everything is stable, we can address secondary factors. If a patient is going blind, what I most want to do is lower his IOP so his glaucoma does not get worse.

"I look at efficacy in terms of how many times a day the medication is needed. After that, I look for safety and comfort."

—Jorge A. Alvarado, MD

Alvarado: In my practice, I look at efficacy in terms of how many times a day the medication is needed. After that, I look for safety and comfort. So I usually choose a once-a-day medication. Then I look at the effect. I want a 20% reduction in pressure. If I do not get that 20% or if 20% is not sufficient, then I look at the once-a-day medications to see which one is most likely to achieve the target pressure.

Katz: There is a law of the jungle with the glaucoma products. We are always evaluating safety and tolerability, but if a drug does not lower pressure a good amount, then we do not use it. ■

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Reformulations and Fixed Combinations: A Look at the Future

With adherence to therapy an ongoing concern, learn how these glaucoma specialists customize treatment to reach the target endpoint more quickly.

Katz: Most of the excitement in glaucoma medications lately has been generated by reformulations of existing products, such as brimonidine Purite (Alphagan-P; Allergan, Inc., Irvine, CA) and travoprost Sofzia (Travatan Z; Alcon Laboratories, Inc., Fort Worth, TX).

Now, we have the FDA-approved fixed combination brimonidine/timolol (Combigan; Allergan, Inc., Irvine, CA). What do these combinations mean to you in your practice?

SIMPLICITY WITH THE NEW "HEAVY HITTERS"

Noecker: The hot topic today, and probably always, in glaucoma therapy, is compliance. We all want to achieve the most efficacy with the fewest number of drops.

I also think less drug is more. With the new combination therapies, we can reach our clinical endpoints more quickly and efficiently than we would by trying every class and perhaps adding one more drug this year and another next year. A combination drug is a different tool to help us achieve our therapeutic endpoints.

Samuelson: I have always felt good prescribing a prostaglandin drug, which I consider a heavy-hitter of glaucoma medications. For patients who cannot use prostaglandins, or for whom that is not enough, it is nice to have another heavy-hitter, such as a combination agent. With a combination, I know I will get a fairly profound drop in pressure as compared to monotherapy.

Katz: I think what we are suggesting is that we should be more aggressive than we have been in the past, and that we need to adhere to a tougher standard in terms of goals and target pressures.

"I think what we are suggesting is that we should be more aggressive than we have been in the past, and that we need to adhere to a tougher standard in terms of goals and target pressures."

—L. Jay Katz, MD

SHIFTING TREATMENT PARADIGM

Katz: You all use the prostaglandins as first-line therapy in the majority of patients. How do you decide which prostaglandin to use? Do you use all of them?

Noecker: It is a judgment call. If my patient is an ocular hypertensive, who has never taken an eye drop, and I think he will not tolerate hyperemia, I might try latanoprost first because, in my experience, it has the least amount of short-term push-back in terms of initial hyperemia. If I have another patient who has advanced glaucoma and requires IOP reduction immediately, I usually go with bimatoprost (Lumigan; Allergan, Inc., Irvine, CA). I will explain to the patient that he might have some hyperemia in the short term, but it should resolve quickly.

The best scenario for travoprost with Sofzia is a patient with an obviously compromised ocular surface—a post-PK patient or someone with peripheral corneal neovascularization or significant meibomian gland disease, for example.

I tend to switch within a class at least once. If a patient starts with latanoprost but did not achieve our goal, then it is worthwhile to try bimatoprost.

Alvarado: I do exactly what Dr. Noecker just described. I think it is easier to begin with latanoprost and then, if you do not get the efficacy you want, switch to bimatoprost. The patient has experienced the effect of the prostaglandin analog, and he or she may be more accepting of the hyperemia and some of the discomfort of bimatoprost when it is used as a second agent.

I frequently see patients referred from the Proctor Foundation, which sees mainly patients with inflammation (uveitis), so I do get a lot of secondary inflammatory glaucomas. For many of those patients, I prescribe travoprost Z. Once I leave the prostaglandin class, my next medication is dorzolamide/timolol (Cosopt; Merck & Co., Inc., Whitehouse Station, NJ), once a day.

Samuelson: I typically start with latanoprost and work my way up the tolerability spectrum as needed. I demand a good response—20% minimum. If I do not get that, then I switch. I am a strong believer in switching within a class, at least within the prostaglandin class. Patients' responses can differ, and there are enough differences in how the prostaglandins are absorbed and how they interact with the receptors, that I will switch within this class.

"I am a strong believer in switching within a class, at least within the prostaglandin class."
—Thomas W. Samuelson, MD

Katz: I know our preference is to keep patients on one drop a day whenever possible to improve adherence to medical therapy at its optimum. But let's say you are not getting the response you want. Dr. Alvarado said he will switch to a fixed combination of dorzolamide/timolol as the next step. We recognize that every patient is different, but, as a general rule, what is your next step in adjunctive therapy?

Samuelson: I offer—or at least talk about—laser earlier than I used to.

Katz: I agree that this is an appropriate time to offer laser therapy. It eliminates any adherence issues or concerns about side effects. But what is the drawback? Why don't you do that first line or second line for every patient?

LASER THERAPY—WHEN?

Samuelson: I discuss laser as initial therapy with a higher percentage of patients now than in the past. I am fairly careful about how I word the discussion, because I want the patient to make the decision without too much direction from me. That said, patients often are looking for a recommendation rather than a list of choices.

I start with medicines, but there is a growing trend for laser for various reasons, not the least of which is to eliminate concerns about compliance. I do not offer laser to glaucoma suspects. If I have a suspect whose pressure is high enough that I feel I should treat it to lower the risk, I almost always treat with medicines. If a patient has true field loss, definable disc damage or nerve fiber layer damage, then I will discuss the laser earlier.

Katz: It sounds as if a fairly large population of patients in your practice do not have laser therapy first line or second line, even though you talk to them about it. Why does that not occur?

Samuelson: Frankly, I do not like surgical procedures that have 25% or even 20% failure rates. It is one thing to switch a patient from a drop that did not work. It is another thing to do an interventional procedure or laser surgery and have it not work. Remember, too, that most of the laser procedures we do are on patients who are taking one, two or three drops. I think the efficacy falls off if laser is the fourth thing you try.

Katz: It is a complex interaction with the patient, particularly if patients have preconceived, and possibly incorrect, notions about laser treatment. Another drawback has been that laser stops working, and you end up talking about medical therapy again. What has been your experience, Dr. Alvarado?

Alvarado: I have been treating with the laser for 7 years, and I cannot think of one patient I have harmed or made worse by using it. So I always tell patients there is no long-term, permanent negative effect. On the other hand, the 20% failure rate is an issue. It relates to the fact that we do not yet have the proper protocols for treating patients with the laser.

Katz: Dr. Noecker, you have done a lot of work with selective laser trabeculoplasty (SLT). How does that fit in?

Noecker: I consider the laser one more tool we can use to treat glaucoma. I put it at about the same level of the treatment algorithm as medications. I am an advocate of SLT, but it does not work for every patient. Just like medications, SLT falls short in some cases, so you must be prepared to use every option at your disposal.

Katz: I think laser trabeculoplasty is being done earlier today, and it probably makes good sense because, as Dr. Samuelson mentioned, if you are using it after four or five medications, it will not work particularly well. It also will not eliminate the need for medicine for a lot of people. It might decrease the medication load, but medical therapy still will be required for most patients whether you use laser or not.

I will briefly mention filtration surgery. We know there are serious interim and postoperative complications with it. The Collaborative Initial Glaucoma Treatment Study (CIGTS) has shown that a patient who is on fairly aggressive medical therapy and maintains a target pressure seems to do just as well over a 5-year period using medications as opposed to going straight to surgery.[1] So even though I am a glaucoma surgeon, I do not offer filtration surgery as as initial therapy to 99.99% of my patients, and the rest of the panelists seem to agree.

Let's move to the next step. We have talked about prostaglandins and possibly laser therapy being introduced. What is the next medical treatment you will consider after prostaglandins?

ADJUNCTIVE MEDICAL THERAPY

Noecker: The traditional choices include a beta-blocker, an alpha-2 agonist or a topical CAI. When used as monotherapy, I would rank their efficacy in that order.[2,3] In an adjunctive role, the differences in efficacy are not as pronounced. Thus, the therapeutic decision may be based more on safety or tolerability.

Historically, beta-blockers have not added significantly to the effect of prostaglandin analogs, and a number of studies have looked at this over time, both as separate agents and in combination preparations.[4–6] What's more, there are systemic safety issues, such as bradycardia or bronchospasm, for some patients with beta-blockers that we may want to avoid.

The efficacy of the alpha-2 agonist brimonidine in an adjunctive role is fairly consistent, and the tolerability with the new formulation with Purite tends to be very good.[7] So I tend to use brimonidine Purite most often in my practice.

There is less tolerability on a marginal cornea with the topical CAIs, and if you dose twice a day, there may be a difference in peak and trough profiles just as with alpha agonists.

We all develop our patterns and customize our first-line and adjunctive therapies. We can talk about averages, but the average does not always help.

Katz: We do tailor treatment according to a host of factors—ocular, systemic, patient preference, your preference. But in the typical patient, what do you use?

Noecker: More often than not, I will use brimonidine with Purite as the first added agent.

Samuelson: I would request two categories. For a patient with severe disease or poorly controlled pressure, I will break with tradition and give a fixed combination next to ramp up therapy fast.

If I have a patient who is showing subtle nerve fiber layer changes or field changes, I want to tweak his therapy. Sometimes, I will prescribe the once-a-day in the morning beta-blocker and the once-a-day at night prostaglandin. That combination is difficult to beat in terms of simplicity, and there are patients who need simplicity. Just as often, I might use brimonidine with Purite or a CAI.

Katz: What is interesting is that you have departed from the standard treatment paradigm. You and Dr. Alvarado say you will use fixed combinations at least in some of your patients.

Samuelson: Dr Katz, do you sometimes break tradition and use the combination earlier?

Katz: Yes, absolutely. The directive has always been to use the least amount of medication to achieve the desired therapeutic response. But the practicalities are that you will lose the patient a little bit if you keep changing his therapy. So I have cut to the chase more, although not in every patient.

Let's say a patient is doing very well. You can either continue, or you might say, "You have done so well. Maybe we can get by with less medication." That is a much more positive experience for the patient than saying, "We need to add another medication because you are still failing."

Samuelson: Dr. Alvarado, you mentioned dosing the dorzolamide/timolol combination once a day. How much better is that combination once-a-day than a once-a-day beta-blocker alone, for example?

Alvarado: I am convinced that the dorzolamide/timolol combination is the second most powerful agent we have available, second only to prostaglandins. I have believed that for decades, and I re-examine that belief every time I prescribe it. I have not found a great deal of evidence to make me sway from that belief.

I have not used the brimonidine/timolol combination yet. I plan to use a prostglandin first and then try one or the other fixed combination to compare them. Brimonidine is my third drug and CAIs are last.

The only difference in my approach to a patient who is severely affected and one who is not so badly affected is

that I move to surgery and/or laser very quickly. If there is any evidence of cataract, I do a combined procedure. I actually seek cataract to allow me to bring a patient to the operating room.

Katz: What is maximum medical therapy before you move to surgery in the typical patient?

Alvarado: Two bottles, three medications.

Noecker: I would say bimatoprost, brimonidine/timolol and probably brinzolamide.

Samuelson: Four drugs, three bottles for me.

Katz: For me, too. I agree with you all. According to some of the older literature, adding a fourth medication is not great in terms of long-term success.[8] If a patient has failed medical therapy and laser, you probably have lost the ballgame after the three medications, and you can start the laser and surgery discussion. I would likely move on to the 'atomic blast' approach that Dr. Alvarado described.

Samuelson: The combined procedure has been my favorite operation over the years, although I do fewer now than I did 5 years ago. It is a chance to lower pressure and improve vision. I think cataract extraction alone is probably the single most commonly performed glaucoma procedure. I think it does lower pressure more than we have realized.

Katz: So if a patient is well controlled medically—or even if his pressure is slightly elevated—and he has a cataract, will you do just a cataract extraction?

Samuelson: It depends on the severity of the disease. If it were my eye and I had a visually significant cataract and I was doing well on glaucoma drops, I would want you to remove my cataract and deal with the pressure later as needed. If I need to continue a well-tolerated medicine postoperatively and it keeps the pressure low enough, that would be perfectly fine.

FIXED COMBINATIONS: LOOKING AHEAD

Katz: We started talking about fixed combinations, specifically the newest one—brimonidine/timolol—and we have come full circle. Here are two drugs with known efficacy and safety profiles, and now they are available together in one bottle. From all the data that have been presented at meetings and from early clinical experience in the United States, safety and tolerability profiles have improved.[9] So repackaging existing drugs seems to have made a powerful bottle of medication.

"We can best treat our patients by minimizing what we ask them to do, what we expose their ocular surface to, and what we expose them to systemically."
—Robert J. Noecker, MD, MBA

Samuelson: I like the idea that the beta-blocker may improve the tolerability of the fixed combination of brimonidine/timolol. But that needs to be clearly proven. I have a hard time believing that my patients were not on beta-blockers all those years when I was seeing brimonidine allergy. But maybe packaging them together will improve tolerability. The Canadian experience, based on my conversations with colleagues practicing there, seems to support that. I am hopeful that is the case because it will be beneficial to have another heavy-hitter in glaucoma management.

Noecker: One of the overriding themes of our discussion today is: Things are not as simple as they appear to be. When we think about formulations and our ability to predict outcomes based on past experience, either on the ocular surface or in terms of efficacy, we really do not know until we take them into clinical practice because of relatively subtle or previously assumed unimportant factors.

We get smarter over time as we get more therapeutic experience, and it is nice to have all these options. We can best treat our patients by minimizing what we ask them to do, what we expose their ocular surface to, and what we expose them to systemically. ■

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CME QUESTIONS

1. Which of the following is considered a prodrug?
a. Alpha agonist
b. Carbonic anhydrase inhibitor (CAI)
c. Dipivefrin (Propine; Allergan, Inc., Irvine, CA)
d. Beta-blocker

2. Which of the following contains the least amount of benzalkonium chloride (BAK), 0.005%?
a. Timolol (Timoptic; Merck & Co. Inc., Whitehouse, NJ
b. Bimatoprost (Lumigan; Allergan Inc., Irvine, CA)
c. Latanoprost (Xalatan; Pfizer, Inc., New York, NY)
d. Dorzolamide (Trusopt; Merck & Co. Inc., Whitehouse, NJ)

3. Which of the following is a stabilized oxychloride compound that breaks down quickly when exposed to sunlight?
a. BAK
b. Purite
c. Sofzia
d. Sorbic acid

4. A study by Alvarado and colleagues suggests that perhaps one way to lessen the incidence of untoward adrenergic agonist reactions might be to treat patients concurrently with which of the following?
a. Alpha agonist
b. CAI
c. Prostaglandin analog
d. Beta-blocker

5. With regard to surface sensitivity, the active molecule of which of the following is probably most responsible for allergy?
a. Alpha agonist
b. CAI
c. Prostaglandin analog
d. Beta-blocker

6. In terms of mechanism of action, which of the following can affect the endothelial cell pump function, possibly leading to corneal edema?
a. Alpha agonist
b. CAI
c. Prostaglandin analog
d. Beta-blocker

7. Hyperemia associated with which of the following seems to be due to the action of the drug on the vessels and tends to be short term?
a. Alpha agonist
b. CAI
c. Prostaglandin analog
d. Beta-blocker

8. Initial studies of which of the following glaucoma preparations showed that changing the preservative and some other components, and increasing the pH may have enhanced penetration of the molecule into the anterior chamber?
a. Timolol
b. Bimatoprost
c. Latanoprost
d. Brimonidine Purite

9. According to Robert J. Noecker, MD, MBA, which of the following glaucoma drops is best suited to a patient with an obviously compromised ocular surface, such as a post-PK patient or someone with peripheral corneal neovascularization or significant meibomian gland disease?
a. Travoprost Sofzia (Travatan Z; Alcon Laboratories, Inc., Fort Worth, TX)
b. Latanoprost
c. Bimatoprost
d. Timolol

10. In the opinion of Thomas W. Samuelson, MD, which of the following is probably the single most commonly performed glaucoma procedure?
a. Selective laser trabeculoplasty
b. Filtration surgery
c. Cataract extraction
d. Laser iridotomy

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