Optimizing the Use of Beta-Blockers in Glaucoma Therapy

A ROUNDTABLE DISCUSSION HELD DURING THE ANNUAL MEETING OF THE AMERICAN GLAUCOMA SOCIETY, MARCH 2008

FEATURING:
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Katz: We are going to start with an overview of medical therapy for glaucoma. As glaucoma specialists, we tend to be minimalists, because we do not like to prescribe drugs that patients have to use more than twice a day. More frequent dosing can lead to complaints from patients and poor adherence. We are also concerned about the efficacy, safety, and tolerability of drugs as well as the cost of the medications we prescribe. What can patients afford to buy? What drugs are included in their insurance companies’ formularies? These factors affect how we treat glaucoma on a daily basis.

Prostaglandin analogs have recently emerged as first-line therapy for most glaucoma patients in the US. We still use beta-blockers as first-line drugs in certain patients who cannot use prostaglandins, either because they do not respond to this class of drugs or because they are concerned about prostaglandins’ side effects. Beta-blockers are most commonly used as second-line therapy, along with alpha-
agonists, topical carbonic anhydrase inhibitors, and fixed-combination drugs.

We have learned, however, that medical therapy is less likely to be effective in the long term if patients use more than two or three medications at one time.\(^1,2\) We must therefore choose adjunctive medications that will effectively lower IOP with the fewest doses per day.

Since 1996, no new drug classes have been introduced into the glaucoma arena, but we have seen new formulations of familiar drugs. Manufacturers now offer prostaglandin analogs that are not preserved with benzalkonium chloride (BAK), and gel-forming solutions allow patients to use beta-blockers only once a day. In 2004, Ista Pharmaceuticals, Inc. (Irvine, CA), introduced Istalol (timolol maleate ophthalmic solution 0.5%), a once-daily beta-blocker that is formulated with potassium sorbate.

Keeping these points in mind, I would like to discuss which beta-blockers you use in your practices, their pros and cons, and how you prescribe them.

**COMPARING FORMULATIONS**

**Herndon:** I agree with Dr. Katz that prostaglandins are still the first line of therapy for most of our patients, because they are very well tolerated. The problem then becomes, what is the best second-line agent? I like to use beta-blockers for patients who can tolerate them, because their efficacy is well documented.\(^3\) For the past 10 years, I used a gel-forming timolol, because it has a safer profile than the regular ophthalmic formulation, but many of my patients complained of blurry vision. Istalol is a definite improvement in the beta-blocker armamentarium, and it has become my first choice in beta-blocker therapy.

Istalol marries timolol maleate with potassium sorbate. Studies have shown that this combination allows Istalol to achieve a higher concentration in the anterior chamber more quickly than generic and other name-brand formulations of timolol.\(^4\)

**Katz:** Could you elaborate on the safety aspect, Dr. Herndon?

**Herndon:** Many years ago, investigators compared the physical performance of healthy men randomized to receive timolol solution and timolol gel. They found that those who used the gel-forming solution had a greater capacity for exercise than those who used the ophthalmic solution. The men randomized to receive timolol gel also had lower systemic levels of the drug.\(^5\) Although I have not seen a similar study evaluating the effect of Istalol on exercise capacity, Mundorf et al\(^6\) showed that Istalol produced lower serum concentrations of timolol than a generic formulation. Based on these studies, I think we can safely extrapolate that a lower systemic absorption of timolol is safer for patients.

**Bacharach:** I would like to mention another double-masked, crossover evaluation of Istalol conducted by Mundorf et al.\(^7\) During this trial, the investigators randomized 12 healthy volunteers to use Istalol (n = 6) or the standard ophthalmic formulation of timolol maleate (n = 6) for 8 days. The patients in the Istalol group received an exaggerated dose of the drug (twice daily) to match the treatment regimen followed by those in the timolol group. After a 7-day washout period, the investigators switched the patients to the opposite treatment (ie, those who used Istalol instilled the standard formulation of timolol for the next 8 days and vice versa).

Although the investigators administered Istalol at twice the clinical dose, the drug’s systemic bioavailability at the end of the study was similar to that observed with the twice-daily dosing of timolol maleate ophthalmic solution. In fact, the trough predosing levels of plasma were statistically lower with the Istalol than with the timolol maleate wing.

**Katz:** The ocular tolerability of beta-blockers has generally been good. Are there any differences in tolerability with various formulations? Do they cause different symptoms such as burning and stinging? You mentioned that the gel was associated with blurry vision, Dr. Herndon.

**Herndon:** Patients complained of blurry vision with timolol gel. Although I have not observed a similar problem with Istalol, some of my patients have experienced ocular burning with this drug. Mundorf et al found that Istalol was associated with more burning than regular timolol.\(^7\) During the past 2 or 3 years however, very few of my patients have discontinued this drug because of that sensation. I tend to tell them that they may experience some ocular discomfort when they start using the drug, and so far, this effect has not been detrimental to my practice.

**Bacharach:** In my experience, patients can avoid the initial ocular stinging they experience with Istalol if the drug is chilled. I also explain that the component that causes this minimal discomfort—potassium sorbate—also improves the drug’s penetration and effectiveness. I find that providing patients with this information improves their understanding of how the drug works and their compliance with the recommended dosing schedule. Furthermore, symptoms of ocular discomfort are usually self-limiting, because many patients eventually develop corneal anesthesia with the chronic use of beta-blockers.\(^8\)

Patients generally tolerate the drug well, however, and none of the patients participating in the pivotal US clinical trials exited the studies due to ocular discomfort.\(^7\)

**Noecker:** I would like to expand on one of Dr. Herndon’s comments. We need to be aware of the differences
between name-brand and generic timolol, and even between generic formulations of timolol in terms of patients’ tolerance and the drugs’ efficacy. My patients experienced more blurry vision and ocular discomfort when they used a generic gel-forming timolol than when they used a name brand. Furthermore, they were more likely to get the generic, even if I wrote a prescription for the name-brand drug. I therefore stopped prescribing name-brand gel-forming timolol approximately 10 years ago.

**ROLE OF POTASSIUM SORBATE IN ISTALOL**

**Katz:** Let’s talk about the role of potassium sorbate in Istalol. How does this ingredient improve penetration?

**Bacharach:** Potassium sorbate increases the bioavailability of timolol by linking the drug’s active ingredient to sorbitol, a medium-chain fatty acid (Figure 1). Higashiyama et al found that this bond between the cationic drug (timolol) and the anionic compound (sorbic acid) increases the drug’s lipophilicity and improved its ability to penetrate the corneal epithelium. In an animal model, the concentration of Istalol in the aqueous and its area under the curve were more than twofold higher than those of timolol maleate solution at all sampling intervals (Figure 2). The investigators also reported that the maximal concentration of Istalol in the subjects’ aqueous humor was similar to that achieved by Timoptic-XE gel (Merck & Co, Inc., Whitehouse Station, NJ).

As some of the panel members have already mentioned, increasing the bioavailability of topical beta-blockers could potentially reduce the incidence of undesirable systemic side effects. I believe that the addition of potassium sorbate gives Istalol unique qualities that differentiate the drug from generic beta-blockers. In fact, the FDA has given Istalol with potassium sorbate a “BT” rating, which prevents pharmacists from substituting generic formulations of timolol maleate for the name-brand drug.

**GLAUCOMA DRUGS AND THE OCULAR SURFACE**

**Herndon:** We glaucoma specialists are paying more attention to the health of the external eye than we did 2 years ago, so we are using drugs and preservatives that are less likely to irritate the ocular surface. I try to use products that have low levels of BAK. I also look at my patients’ eyelids, corneas, and tear films closely for any signs of ocular surface disease.

**Noecker:** We assume that all formulations have similar amounts of BAK, but Istalol contains less of this preservative than typical generic versions of timolol. As I mentioned earlier, patients are more likely to get generic than name-brand timolol from their pharmacies, even if you specifically prescribe a branded formulation. Getting a name-brand drug sometimes makes a difference.

**GLAUCOMA TODAY**

**Katz:** Dr. Vold, how do you use beta-blockers in your practice?

**Vold:** We all agree that there has been a big push toward prostaglandins as first-line therapy, but the sequence in which we use second-line drugs such as beta-blockers, carbonic anhydrase inhibitors, and alpha-2 agonists is still disputed. Beta-blockers have a bad reputation for not working well with prostaglandins, but that is not the case for all patients. Compliance improves when physicians prescribe an adjunctive drug that patients have to use once versus two or three times a day.

In addition to dosing frequency, the cost of drugs, patients’ forgetfulness, their physical ability to instill the eye drops, the risk of systemic side effects, and the incidence of local adverse effects such as blurry vision, ocular burning/stinging and hyperemia could affect patients’ compliance with prescribed therapy. Every patient is different. I try to tailor adjunctive therapy to their individual needs.
Katz: In certain cases, I use Istalol as an alternative first-line agent. Between 10% and 20% of patients either do not respond to or cannot tolerate prostaglandin analogs. I also sometimes hesitate to prescribe prostaglandin analogs for patients who only need to use IOP-lowering drugs in one eye. A once-daily beta-blocker like Istalol may be a more appropriate first-line agent for these individuals.

Noecker: I agree with Dr. Katz. The potential effects of prostaglandin analogs—including hyperemia, trichomegaly, periorcular hyperpigmentation, and changes in iridal color—could be more noticeable and are more likely to be problematic in patients who require monocular therapy. I tend to prescribe Istalol to these patients first, because it is well tolerated and effectively lowers IOP. Using the drug in only one eye means the patients are getting a lower dose and thus could have a lower risk of developing systemic side effects than those who need bilateral therapy.

Vold: Istalol is an excellent first-line therapy for patients who are vulnerable to the unwanted pigmentation and eyelash growth that can occur with prostaglandin analogs. I have found that young men often prefer to use a topical beta-blocker versus a prostaglandin as first-line therapy, because they want to avoid these cosmetic changes.

Bacharach: I avoid prostaglandin analogs not only in patients who could be affected cosmetically (Figure 3) but also in those who could be vulnerable to the drugs’ inflammatory potential. For example, prostaglandin analogs could exacerbate preexisting cystoid macular edema in patients with uveitic glaucoma who are aphakic or who have a history of complicated cataract surgery. The literature describes instances in which topical prostaglandin analogs reactivated corneal dendrites. I therefore also avoid using these drugs in patients who have a history of herpetic keratitis. Instead, I would likely prescribe Istalol as primary therapy.

In addition, I prefer to use Istalol as first-line therapy for patients who previously underwent laser trabeculoplasty, because the procedure’s effect on aqueous outflow is mechanistically synergetic with the beta-blocker’s reduction of aqueous inflow. Istalol also works as primary therapy after filtration or tube surgery in which the bleb has become encapsulated. Because the beta-blocker decreases the flow of aqueous through the bleb, it has in some cases reportedly reduced encapsulation and dramatically lowered IOP.

Katz: As Dr. Bacharach pointed out, Istalol offers good penetration into the anterior chamber, which supports once-daily dosing. I think the potassium sorbate formulation makes enough of a difference that patients can benefit from one dose per day.

Herndon: Scientific research supports the effectiveness of once-daily Istalol. Some studies suggest that alpha-agonists or carbonic anhydrase inhibitors may be better adjunctive agents to prostaglandins, but these results are based on stringently controlled trials in which patients are committed to using the second-line drugs two or three times a day. Real-world experience shows that patients are more likely to use drugs that require fewer doses. Prescribing Istalol in the morning and a prostaglandin in the evening to my patients appears to improve their compliance with IOP-lowering therapy.

Bacharach: I agree with Dr. Herndon that the two-drop regimen works well clinically. Patients’ compliance increases dramatically when they do not have to instill a third drop in the middle of the day.

CONSIDERING COST
Katz: Dr. Vold, you mentioned that you consider cost when prescribing adjunctive drugs to your patients. Can you tell us more about how this factor influences your therapeutic choices?

Vold: I have been studying the effect of cost on patients’ compliance with glaucoma therapy for 10 years. The price of drugs is a big issue for many patients, especially in a climate of escalating healthcare costs. For instance, a once-daily generic beta-blocker costs...
patients approximately $150 per year. This is a relative bargain compared with brimonidine Purite (Alphagan P; Allergan, Inc., Irvine, CA), which can cost more than $800 when used three times a day for a year.16

Our analysis showed that once-daily Istalol costs approximately $200 per year; only slightly more than a generic beta-blocker and considerably less than the $400 to $500 a patient would spend for a year’s worth of a prostaglandin analog. This can be a huge difference for some people. I want to provide the most effective care at the lowest possible cost.

Katz: We always assume that the generic formulations are cheaper than branded drugs. As Dr. Noecker pointed out earlier, however, not all generics are the same, and their efficacy and tolerability may vary. My staff and I periodically check the price of name-brand drugs in our area. Patients appreciate it when we say, “I know this drop is going to be expensive, but I think it is important that you get it,” and then we direct them to the best place to buy it.

Vold: I frequently prescribe name-brand Istalol for its efficacy and tolerability, even though it may cost slightly more than generic timolol. I am sure we all have received phone calls from patients who were angry about the price of a medication we prescribed for them. We can help prevent such complaints by talking to our patients about what they should expect to pay for their prescriptions. I think this makes us better doctors and helps us to meet the needs and expectations of our patients.

Herndon: That is an interesting scenario, Dr. Vold. At the same time, if a patient comes to me and says that he would prefer to use generic timolol because he cannot afford to buy a name-brand drug, I will tell him to do whatever he needs to lower his IOP. I think Istalol is safer than generic beta-blockers, but it will only be effective if the patient fills and uses the prescription.

Katz: When we talk about our patients’ finances, we also need to consider how many medications they use for systemic conditions. Everybody seems to be taking a statin as well as something for their blood pressure and nerves. Somebody has to pay for that, namely the patients. If they cannot afford all of their drugs, they may not adhere to their glaucoma therapy.

Alan Robin, MD, observed that refill rates dropped when physicians added a second medication to a patient’s regimen—not only for the second medication, but also for the first.17 The more drugs prescribed, he noted, the less likely the patient is to fill them at the right intervals and use them properly at home. I think the financial burden of paying for multiple drugs can only exacerbate such a situation.

Figure 3. The hyperemia in this patient’s right eye resolved after he switched from monocular therapy with a prostaglandin analog to Istalol.

THE FUTURE OF BETA-BLOCKERS

Katz: Do you think we will still be treating glaucoma with beta-blockers 5 or 10 years from now?

Herndon: I think beta-blockers will still be here. A meta-analysis studies of all classes of glaucoma drops showed that beta-blockers are number two in terms of efficacy after prostaglandin analogs, and they lower IOP by 26% to 27%.3 I do not see another drug on the horizon that is set to replace beta-blockers in the near future.

Bacharach: Beta-blockers’ mechanism of action is also complementary to other IOP-lowering medications and therapies. I believe that is why fixed combinations often pair a beta-blocker with another class of glaucoma medication.

Noecker: The beta-blockers that are currently available are better than those we had 30 or even 10 years ago.

Vold: I agree. Some drugs in the pipeline may have different mechanisms or longer durations of action, but I still see a role for beta-blockers in the foreseeable future. Given the cost of drugs, I would not be surprised if there were more pressure on us to prescribe beta-blockers in the next few years.

Katz: As Dr. Herndon mentioned, beta-blockers are still the second most prescribed class of glaucoma drugs. I agree with all of you that they are not going to disappear in the next 5 to 10 years.

References
Fair Use Statement

Istalol is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock, or hypersensitivity to any component of this product.

The most frequently reported adverse experiences have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional events reported with Istalol at a frequency of 4% to 10% include blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching, and decreased visual acuity.

Store Istalol at 15º to 20º C (59º to 77º F).