

ARVO 2010

Some of the highlights of this year's meeting.

BY ALBERT S. KHOURI, MD, AND VINNIE P. SHAH, MD

This article summarizes some of the interesting projects presented at the recent annual meeting of the Association for Research in Vision and Ophthalmology.

CONSISTENCY OF DIURNAL IOP PATTERNS OVER TIME

Once clinicians perform a diurnal curve, they often assume that it reflects the IOP behavior for that patient. Tony Realini, MD, MPH, and colleagues presented a study that addressed the following intriguing question: does IOP follow the same diurnal pattern from day to day? They conducted diurnal IOP testing in two sessions 1 week apart on 47 patients with treated open-angle glaucoma. IOP measurements were obtained every 2 hours from 8 AM to 8 PM using Goldmann tonometry.

Their analysis used the intraclass correlation coefficient (ICC) to measure the agreement between IOP at each time point on the first visit and the IOP at the same time point 1 week later. The ICC has values between -1 and +1; values below 0.4 represent poor agreement, between 0.4 and 0.75 represent fair-to-good agreement, and above 0.75 represent excellent agreement. In general, they reported only fair-to-good agreement of IOP measurements at the same time of day 1 week apart, with ICC values ranging from 0.45 to 0.71 in right eyes (results in left eyes were not reported but were stated to be similar). The group also assessed the agreement of changes in IOP between time points (eg, comparing change between 8 AM and 10 AM at the first visit and between 8 AM and 10 AM 1 week later). They found uniformly poor agreement, with ICC values ranging from -0.05 to +0.38 (negative ICC values indicate agreement worse than that expected by chance alone).

What are the clinical implications of these findings? According to its authors, the study suggests that, even if clinicians perform a single-day diurnal IOP test on a given patient, they still may not know much about his or her IOP behavior on other days. Although there is still value in knowing a patient's peak and range of IOP over time, Dr. Realini said, a single-day diurnal IOP assessment may not fully capture the breadth of diurnal variability in IOP.¹

"Calculating individual risk for the development of POAG [was] simpler and equally accurate using IOP and [central corneal thickness] as measured, rather than applying any algorithm to correct IOP for CCT."

CENTRAL CORNEAL THICKNESS

The prediction model for the development of primary open-angle glaucoma (POAG) from the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study includes central corneal thickness (CCT) in addition to age, IOP, pattern standard deviation, and cup-to-disc ratio. Measuring CCT has become the standard of care, as clinicians try to stratify the risk of conversion among glaucoma suspects. It is also well determined that CCT affects IOP measurements with Goldmann tonometry. After refractive surgery, for example, IOP is often underestimated as the cornea becomes thinner.

Many algorithms have been proposed for correcting IOP based on CCT. James Brandt, MD, and colleagues from the OHTS Group and European Glaucoma Prevention Study Group asked whether adjusting baseline IOP for CCT increases the accuracy of the prediction model for the development of POAG. Dr. Brandt explained that they ran the same hazards model and changed only whether the IOP was or was not adjusted for CCT. In the models that included IOP adjusted for CCT, the c-indices (discrimination) ranged from 0.763 to 0.770, no better than the original prediction model (0.774). They concluded that CCT is a powerful risk factor that relates to biomechanical properties of the eye beyond the purely observed effects on Goldmann tonometry measurements. Their study found that calculating individual risk for the development of POAG is simpler and equally accurate using IOP and CCT as measured, rather than applying any algorithm to correct IOP for CCT.²

POAG PATIENTS' RISK FOR AN IOP SPIKE AFTER PHACOEMULSIFICATION

Why do some POAG patients experience an IOP spike after phacoemulsification, whereas others do not? Mark Slabaugh, MD, and colleagues from the Department of Ophthalmology at the University of Washington in Seattle performed a retrospective review to try to answer this question. They identified 80 consecutive patients with POAG who underwent uncomplicated primary cataract extraction via phacoemulsification. All patients were prescribed acetazolamide for the first 24 hours instead of their usual topical IOP-lowering agents. The vast majority received acetazolamide 500 mg that evening and again in the morning, but a few only received the drug (500 mg) that evening. On postoperative day 1, acetazolamide was discontinued, and topical IOP-lowering agents were restarted. The investigators calculated baseline IOP as an average of the IOP at the last three office visits, and they arbitrarily defined an IOP spike as an increase in IOP of 10 mm Hg or more from baseline.

The investigators were surprised to find that 23% of patients had an IOP spike on postoperative day 1, even after an uncomplicated cataract extraction. They then proceeded to examine the variables associated with the elevation. Their analysis showed that the statistically significant variables associated with a postoperative IOP spike were younger age, a preoperatively wider gonioscopic angle (graded by Schaffer classification), myopia, the use of an acrylic (rather than silicone) IOL, and—as expected—failure to use the acetazolamide. These findings highlight clinicians' need to be vigilant in their monitoring of glaucoma patients, even after uncomplicated cataract extraction, because one in five may experience an IOP spike postoperatively.³

SELECTIVE LASER TRABECULOPLASTY

Does the outcome of selective laser trabeculoplasty (SLT) in one eye predict the response in the contralateral eye? A group of researchers from Massachusetts Eye and Ear Infirmary performed a retrospective review of all SLT cases (amount of treatment not specified) performed by three surgeons between 2002 and 2008. Mean follow-up was about 41 months. Success was defined as a drop in IOP of more than 3 mm Hg without the use of any additional medication or surgery. In total, 178 eyes were included. The interval between the two SLT procedures was about 13 months.

Three-quarters of eyes showed the same result, whether success or failure, in the second treated eye. Among eyes with successful SLT (27%), SLT on the second eye was also a success in 87.5%. The opposite sce-

nario was equally true in that, if the first SLT treatment failed in the first eye (73%), it also failed in the contralateral eye (71%). A multivariate logistic regression analysis showed a statistically significantly lower risk of SLT's failure in the second eye when higher energy was used (0.98 mJ in eyes with success, 0.86 mJ in eyes with failure). For each 0.1 mJ of higher laser energy power, the odds were increased by 2.34 in favor of success. Jea et al concluded that higher energy may improve success with SLT in patients in whose first eye the procedure failed. They did not offer an explanation for the high failure rate reported.⁴

Another group from New York Medical College, Indiana University, and the Metropolitan Hospital Center in New York studied the effectiveness of repeat SLT for POAG. Jason Peragallo, MD, described their findings in 19 eyes that received a repeat SLT procedure an average of 500 days after the first SLT treatment. All eyes were on maximal glaucoma therapy. This short-term response study included a comparison of IOP response 6 weeks after the first and repeat SLT procedures. The mean baseline IOP was about 18 mm Hg on maximal therapy. The change in IOP from the first SLT (-2.26 mm Hg) was not statistically different from the change in IOP from the repeat SLT (-1.68 mm Hg). The investigators concluded that repeat SLT was effective at lowering IOP in patients with POAG who previously underwent SLT but that longer follow-up of a larger series will better characterize this response.⁵ Many other groups presented interesting data on SLT's long-term results, higher-energy SLT's efficacy, and IOP spikes after SLT treatment.

DRUG DELIVERY

Several groups of researchers presented work on glaucoma drug delivery systems, although they are still far from direct clinical application. Alina Dumitrescu, MD, and a group of researchers from the University of Iowa, Iowa State University, Yale University, and Case Western Reserve University presented their work on sustained-release timolol microspheres after subconjunctival injection. To evaluate in vivo release characteristics, the investigators studied their delivery system in mice, rabbits, and cats. Aqueous and vitreous samples were collected with measurable timolol from 60 to 100 days after injection. These investigators cautioned that much work still needs to be done, as researchers attempt to find the ideal sustained-release delivery system over longer periods. It was encouraging that no foreign body reaction was noted on histologic and immunohistochemical examination of tissues after the injections.⁶

A second group of researchers from Vanderbilt University worked on nanoparticle-encapsulated delivery of

“[Research on nanoparticles may point to] another realm of possibilities for the delivery of neuroprotective agents to retinal cells.”

brimonidine and travoprost to the eye. Grace Shih and coworkers presented their research utilizing a 53 nano-sponge loaded with the aforementioned two agents that was intravitreally injected into mice's eyes. Before the procedure, elevated IOP was induced by the injection of microbeads into the anterior chamber to block aqueous outflow. An IOP reduction was achieved for 12 days. Another interesting observation, however, was that nanoparticles reached the retina without exhibiting toxic effects and were picked up within retinal ganglion cells. The hope is that this finding may open up another realm of possibilities for the delivery of neuroprotective agents to retinal cells.⁷ □

Albert S. Khouri, MD, completed his residency at the American University of Beirut in Lebanon and his glaucoma fellowship at the University of Louisville in Kentucky. He is currently completing a US residency at the University of Medicine and Dentistry of New Jersey in Newark. Dr. Khouri may be reached at (973) 972-0205; albert.khouri@umdnj.edu.



Vinnie P. Shah, MD, is currently completing her residency at the University of Medicine and Dentistry of New Jersey in Newark.



- Realini T, Weinreb RN, Wisniewski S. Diurnal intraocular pressure patterns are not repeatable in the short term in glaucomatous individuals. Paper presented at: The ARVO Annual Meeting; May 4, 2010; Fort Lauderdale, FL.
- Brandt JD, Gordon MO, Kass MA, et al. Ocular Hypertension Treatment Study Group and European Glaucoma Prevention Study Group. Does adjusting IOP for central corneal thickness improve accuracy of the prediction model for the development of POAG? Poster presented at: The ARVO Annual Meeting; May 4, 2010; Fort Lauderdale, FL.
- Slabaugh MA, Chen PP, Moore DB. Risk factors for post phacoemulsification IOP spike in OAG patients. Poster presented at: The ARVO Annual Meeting; May 4, 2010; Fort Lauderdale, FL.
- Jea S, Pasquale LR, Grosskreutz CL, Rhee DJ. Predictors of success of selective laser trabeculoplasty. Poster presented at: The ARVO Annual Meeting; May 5, 2010; Fort Lauderdale, FL.
- Peragallo JH, Malen M, Lai PC. Effectiveness of repeat selective laser trabeculoplasty on primary open angle glaucoma (POAG) patients. Poster presented at: The ARVO Annual Meeting; May 5, 2010; Fort Lauderdale, FL.
- Dumitrescu AV, Bertram J, Olson LR, et al. In-vivo characterization of sustained release timolol microspheres. Poster presented at: The ARVO Annual Meeting; May 4, 2010; Fort Lauderdale, FL.
- Shih GC, Sternberg MG, Crish SD, et al. Nanoparticle drug delivery to retinal ganglion cells in glaucoma. Poster presented at: The ARVO Annual Meeting; May 4, 2010; Fort Lauderdale, FL.

BETIMOL® (timolol ophthalmic solution) 0.25%, 0.5%

BRIEF SUMMARY

INDICATIONS AND USAGE Betimol® is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

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

WARNINGS As with other topically applied ophthalmic drugs, Betimol® is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failure have been reported following systemic or topical administration of beta-adrenergic blocking agents. Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe cardiac failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Betimol® should be discontinued at the first sign or symptom of cardiac failure. Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma which are contraindications) should in general not receive beta-blocking agents. Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to a major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heart-beat has also been reported. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents is recommended. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of beta-adrenergic agonists. Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS General Because of the potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Betimol®, alternative therapy should be considered. There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, Information for Patients.) Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalized weakness). Beta-adrenergic blocking agents have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms. In angle-closure glaucoma, the goal of the treatment is to reopen the angle. This requires constricting the pupil. Betimol® has no effect on the pupil. Therefore, if timolol is used in angle-closure glaucoma, it should always be combined with a miotic and not used alone. Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions. The preservative benzalkonium chloride may be absorbed by soft contact lenses. Patients who wear soft contact lenses should wait 5 minutes after instilling Betimol® before they insert their lenses. **Information for Patients** Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See PRECAUTIONS, General.) Patients requiring concomitant topical ophthalmic medications should be instructed to administer these at least 5 minutes apart. Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, or cardiac failure should be advised not to take this product (See CONTRAINDICATIONS). **Drug Interactions** Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Betimol® should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. Patients should not usually receive two topical ophthalmic beta-adrenergic blocking agents concurrently. Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Calcium antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided. Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. Injectable Epinephrine: (See PRECAUTIONS, General, Anaphylaxis.) **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity of timolol (as the maleate) has been studied in mice and rats. In a two-year study orally administered timolol maleate (300mg/kg/day) (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose) in male rats caused a significant increase in the incidence of adrenal pheochromocytomas, the lower doses, 25 mg or 100 mg/kg daily did not cause any changes. In a life span study in mice the overall incidence of neoplasms was significantly increased in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Furthermore, significant increases were observed in the incidences of benign and malignant pulmonary tumors, benign uterine polyps, as well as mammary adenocarcinomas. These changes were not seen at the daily dose level of 5 or 50 mg/kg (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). For comparison, the maximum recommended human oral dose of timolol maleate is 1 mg/kg/day. Mutagenic potential of timolol was evaluated *in vivo* in the micronucleus test and cytogenetic assay and *in vitro* in the neoplastic cell transformation assay and Ames test. In the bacterial mutagenicity test (Ames test) high concentrations of timolol maleate (5000 and 10,000 µg/plate) statistically significantly increased the number of revertants in *Salmonella typhimurium* TA100, but not in the other three strains tested. However, no consistent dose-response was observed nor did the number of revertants reach the double of the control value, which is regarded as one of the criteria for a positive result in the Ames test. *In vivo* genotoxicity tests (the mouse micronucleus test and cytogenetic assay) and *in vitro* the neoplastic cell transformation assay were negative up to dose levels of 800 mg/kg and 100 g/mL, respectively. No adverse effects on male and female fertility were reported in rats at timolol oral doses of up to 150 mg/kg/day (21,000 times the systemic exposure following the maximum recommended human ophthalmic dose). **Pregnancy Teratogenic effects:** Category C. Teratogenicity of timolol (as the maleate) after oral administration was studied in mice and rabbits. No fetal malformations were reported in mice or rabbits at a daily oral dose of 50 mg/kg (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Betimol® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** Because of the potential for serious adverse reactions in nursing infants from timolol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric use:** Safety and efficacy in pediatric patients have not been established.

ADVERSE REACTIONS The most frequently reported ocular event in clinical trials was burning/stinging on instillation and was comparable between Betimol® and timolol maleate (approximately one in eight patients). The following adverse events were associated with use of Betimol® in frequencies of more than 5% in two controlled, double-masked clinical studies in which 184 patients received 0.25% or 0.5% Betimol®. **OCULAR:** Dry eyes, itching, foreign body sensation, discomfort in the eye, eyelid erythema, conjunctival injection, and headache. **BODY AS A WHOLE:** Headache. The following side effects were reported in frequencies of 1 to 5%: **OCULAR:** Eye pain, epiphora, photophobia, blurred or abnormal vision, corneal fluorescein staining, keratitis, blepharitis and cataract. **BODY AS A WHOLE:** Allergic reaction, asthenia, common cold and pain in extremities. **CARDIOVASCULAR:** Hypertension. **DIGESTIVE:** Nausea. **METABOLIC/NUTRITIONAL:** Peripheral edema. **NERVOUS SYSTEM/PSYCHIATRY:** Dizziness and dry mouth. **RESPIRATORY:** Respiratory infection and sinusitis. In addition, the following adverse reactions have been reported with ophthalmic use of beta blockers: **OCULAR:** Conjunctivitis, blepharitis, decreased corneal sensitivity, visual disturbances including refractive changes, diplopia and retinal vascular disorder. **BODY AS A WHOLE:** Chest pain. **CARDIOVASCULAR:** Arrhythmia, palpitation, bradycardia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure and cardiac arrest. **DIGESTIVE:** Diarrhea. **ENDOCRINE:** Masked symptoms of hypoglycemia in insulin dependent diabetes (See WARNINGS). **NERVOUS SYSTEM/PSYCHIATRY:** Depression, impotence, increase in signs and symptoms of myasthenia gravis and paresthesia. **RESPIRATORY:** Dyspnea, bronchospasm, respiratory failure and nasal congestion. **SKIN:** Alopecia, hypersensitivity including localized and generalized rash, urticaria.

Rx Only

MARKETED BY: VISTAKON® Pharmaceuticals, LLC
Jacksonville, FL 32256 USA
MANUFACTURED BY: Santen Oy, P.O. Box 33 FIN-33721 Tampere, Finland
November 2006 Version

VISTAKON PHARMACEUTICALS, LLC

Santen

2708BE-013