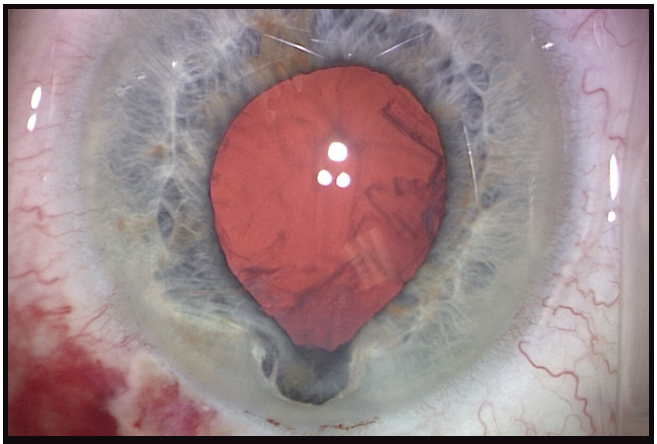
IFIS Severity Varies by Type of Alpha Blocker

DAVID F. CHANG, MD

When it comes to severe intraoperative floppy iris syndrome (IFIS), does the type of alpha blocker make a difference? According to a newly published study, the answer is yes: Severe IFIS is more likely to occur with tamsulosin (Flomax), which is selective for the alpha$_{1A}$ receptor subtype, than it is with alfuzosin (Uroxatral), a nonselective alpha$_1$ antagonist.[1] In addition, the study reports the new finding that moderate to severe IFIS can occur even in patients who have never taken an alpha blocker when epinephrine is omitted from the irrigating solution during phacoemulsification.

Part of what has made tamsulosin the most-prescribed alpha blocker for benign prostatic hyperplasia (BPH) is its receptor selectivity, which reduces the risk of postural hypotension compared with nonselective alpha blockers such as terazosin (Hytrin) and doxazosin (Cardura). However, alfuzosin, the newest nonselective alpha blocker, is considered clinically uroselective in that it rarely causes postural hypotension.

The study. For this multicenter prospective, masked, controlled comparison of the two clinically uroselective drugs, David F. Chang, MD, Cedric Schweitzer MD, and colleagues evaluated 226 eyes. The study was conducted in France, where alfuzosin is more commonly prescribed than in the United States. In an effort to avoid masking or preventing IFIS, intracameral use of epinephrine or phenylephrine was not permitted (including in the irrigation bottle).



IFIS. Severe intraoperative floppy iris syndrome was significantly less likely to occur in patients taking alfuzosin than tamsulosin. Both are clinically uroselective agents.

Severe IFIS—iris billowing and prolapse with 2 mm or more of pupil constriction—was noted in 24 of 70 tamsulosin eyes (34.3 percent), 7 of 43 alfuzosin eyes (16.3 percent), and 5 of 113 control eyes (4.4 percent).

In both a secondary analysis of the control group and a separate substudy of 127 additional eyes in which epinephrine was not added to the irrigation bottle, 14 of 113 control eyes (12.4 percent) and 17 of 127 substudy eyes (13.4 percent) experienced moderate to severe IFIS, which the investigators attributed to the absence of epinephrine.

Mechanism of action. Why does tamsulosin have a greater effect on the iris than nonselective alpha blockers do? Moreover, why does IFIS persist despite discontinuation of the drug?

The answer may involve atrophy of the iris dilator muscle, said Dr. Chang, who practices in Los Altos, Calif. "The first in vitro study of alpha-antagonist pharmacokinetics in the iris dilator muscle suggested that the mechanism of muscle inhibition by tamsulosin was more complex than simple receptor blockade.[2] Other evidence indicates that tamsulosin has a strong binding affinity for iris pigment granules.[3] This, in turn, may cause a long-term 'toxic' effect on the adjacent iris dilator muscle, which then atrophies."

Take-aways. Dr. Chang said, "This study suggests that patients with cataracts who need to take uroselective alpha blockers for BPH may wish to try alfuzosin first. However, regardless of which alpha blocker patients are taking, surgeons must still anticipate IFIS." They also "should recognize that there is a wide spectrum of IFIS severity," he said. "Some eyes in tamsulosin patients may demonstrate the full triad of severe IFIS; others may show little effect. Failure to dilate well is a good indicator for more severe iris dilator impairment, according to this latest study." —*Jean Shaw*

1 Chang DF et al. *Ophthalmology.* 2013 Dec. 5. [Epub ahead of print].
2 Palea S et al. *J Cataract Refract Surg.* 2008;34(3):489-496.
3 Goseki T et al. *J Cataract Refract Surg.* 2012;38(9):1643-1649.

Dr. Chang reports no related financial interests.

EXTRA *MORE ONLINE. For pearls from Dr. Chang and a reading list, see this article online.*

Alternative to Surgery?

Bupivacaine: A Second Injectable for Strabismus

Three decades after expanding the options in strabismus treatment with botulinum toxin A (Botox), a San Francisco researcher thinks he has found something better: the anesthetic bupivacaine.

"This is a practical alternative to surgical correction, much better than Botox alone," said Alan B. Scott, MD, a senior scientist at the Strabismus Research Foundation. "Bupivacaine has an effect which is much more permanent."

For much of the last decade, Dr. Scott and longtime collaborators Joel M. Miller, PhD, and Kenneth K. Danh, BS, have been trying to turn bupivacaine's myotoxicity into a tool for predictably strengthening and shortening ocular rectus muscles. Their first success was documented in a 2007 case study.[1] Now the researchers report confirming the drug's effectiveness for as long as three years in 31 adults with comitant horizontal strabismus (mean deviation: 24.0 prism diopters [PD]).[2]

Study results. A single injection of bupivacaine (0.75 to 3 percent) into the lateral or medial rectus muscle reduced misalignment by an average of 10.5 PD, they reported. (Concentrations higher than 0.75 percent are not commercially available and must be prepared by a compounding pharmacy.)

A second bupivacaine treatment had a lesser effect than the first; consequently, for larger misalignments, the researchers added an epinephrine injection to the bupivacaine and/or a concurrent injection of botulinum toxin into the opposing muscle to increase the treatment impact. "When bupivacaine is used together with 3 to 5 units of Botox, we can typically correct 20 or 25 prism diopters with effects lasting for years rather than for months as with Botox alone," he said.

Complications included overcorrection and diplopia in two patients who initially had small deviations.

Another 42 patients have been treated since the study's conclusion. "We have done 73 patients; and, of those patients, there were some at the very beginning who required repeated injections, and some required surgical correction eventually," Dr. Scott said. "But as we've moved along and increased our dosages, added the epinephrine and its effect of potentiation, we are getting larger and more permanent effects."

Mechanism. Cross-sectional MRI scans showed that damage caused by the bupivacaine was followed by structural changes and remodeling in the healed muscle, which the researchers believe are responsible for the treatment effect.

"The mechanism of effectiveness is that bupivacaine slightly strengthens the muscle, by about 7 percent, and it substantially shortens the muscle," Dr. Scott said. "The muscle is slightly thinned in its anterior portion but thickened in the posterior portion, where most of the contraction happens."

The shorter length appears to be crucial, as demonstrated by computer modeling. "Strengthening the muscle alone would require a doubling or tripling of the size of the muscle in order to create these kinds of alignment changes that we get," Dr. Scott said.

In the clinic. Dr. Scott expressed confidence that the study contains sufficient evidence of effectiveness for ophthalmic surgeons to begin immediately with this off-label use of bupivacaine instead of surgery in adults with moderate comitant strabismus. Use in children, however, is just being explored, he said.

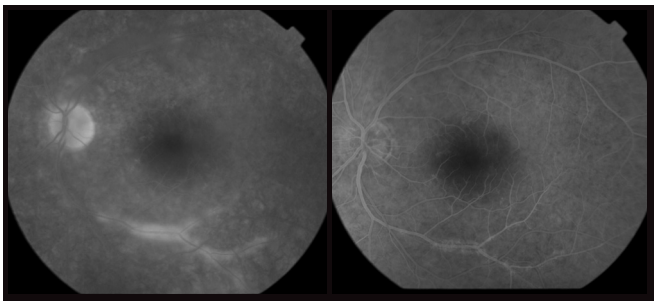
—*Linda Roach*

1 Scott AB et al. *Br J Ophthalmol.* 2007;91(2):146-148.
2 Miller JM et al. *Ophthalmology.* 2013;120(12):2733-2740.

Dr. Scott said he preemptively patented this use of bupivacaine to keep opportunists from patenting it and blocking open access. He said he will neither license the patent for commercial use nor collect royalties.

Uveitis Update

Methotrexate May Be an Alternative for Uveitis



MTX. Before and after treatment with methotrexate.

Methotrexate (MTX) appears to be a reasonable alternative to intravitreal steroids for treating noninfectious uveitis.[1] Intravitreal MTX is particularly useful in patients with a history of intraocular pressure (IOP) elevation in response to steroids, said Simon R.J. Taylor, MD, PhD, clinical senior lecturer and consultant ophthalmic surgeon at Imperial College London.

Dr. Taylor headed a multicenter retrospective study to assess the outcomes of a 400-µg injection of MTX in 38 eyes (30 patients). MTX effectively controlled inflammation and improved vision in 30 of 38 eyes (79 percent). Twenty-two responders (73 percent) enjoyed an extended period of remission with a median time to relapse of 17 months. In keeping with an earlier study that noted the success of reinjection,[2] all but one of the eight eyes that relapsed entered extended remission following a second injection.

No serious ocular adverse events were reported. One patient experienced elevated IOP (28 mmHg). Of the 14 patients who were on systemic corticosteroid treatment before the study, eight (57 percent) were weaned from their steroid regimen.

A meta-analysis of this and Dr. Taylor's earlier study gives a positive response rate of 80 percent and an estimated time to relapse of 17 months. A future study might consider how to predict the responders, Dr. Taylor said.

For now, he wants ophthalmologists to know that the choice of intravitreal therapy in uveitis goes beyond corticosteroids and anti-VEGF agents. "Intraocular methotrexate can deliver very good results in some patients, and the side effect profile appears good."

—Miriam Karmel

1 Taylor SR et al. *Retina.* 2013; 33(10):2149-2154.
2 Taylor SR et al. *Ophthalmology.* 2009;116(4):797-801.

***Dr. Taylor** receives salary support from the UK National Institute of Health Research and unrestricted laboratory support from the Biotechnology and Biological Sciences Research Council, GlaxoSmithKline, and Novartis; is a consultant to Allergan, Novartis, and Santen; and is principal investigator for clinical trials run by Allergan, Bayer, and Novartis.*

Glaucoma Report

Preventing Drainage Device Erosions

Implantation of a glaucoma drainage device (GDD) is often accompanied by at least one additional ocular procedure. But a study conducted at Wills Eye Institute in Philadelphia has identified concomitant surgery (not including placement of a scleral or corneal patch graft to cover the tube) as a risk factor for GDD-related erosions.[1]

"As implantation of glaucoma drainage devices increases in popularity, so do the number of concomitant procedures performed with them," said Valerie Trubnik, MD, now an attending surgeon at Ophthalmic Consultants of Long Island. "The majority of these concomitant surgeries are cataract extractions and pars plana vitrectomies."

To evaluate the potential impact of concomitant surgeries, the researchers reviewed the records of 1,013 patients who had undergone placement of a GDD between 2006 and 2011.

Chart review found complete sets of desired data points and at least six months of follow-up on 339 eyes. Twenty-eight eyes (8.3 percent) had developed conjunctival erosions. Concomitant intraocular surgery was the only variable significantly associated with the development of erosions after GDD implantation.

Dr. Trubnik noted, however, that dry eye syndrome and pseudoexfoliation glaucoma may also be associated with the development of erosions, although these variables did not reach statistical significance in the current study because of the limited number of patients.

Dr. Trubnik and colleagues plan to evaluate these and other variables in a prospective study in a larger patient population. "Drainage device erosion, albeit rare, can lead to severe complications that require challenging management decisions," she said. "Identifying patient-specific risks and procedural risks will help minimize morbidity, expense, and overall time to achieve optimal treatment."

—Marianne Doran

1 Trubnik V et al. *J Glaucoma.* 2013 Dec. 10. [Epub ahead of print].

***Dr. Trubnik** reports no related financial interests.*

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