By Paul McGinn

Ophthalmologists warned about "floppy iris" syndrome

American cataract surgeons have warned their colleagues in Europe and around the world to be on the look out for the so-called "Intra-operative Floppy Iris Syndrome."

The syndrome – which is known by the acronym "IFIS" – is characterised by subnormal preoperative pupil dilation and repeated intraoperative prolapse of a billowing, floppy iris in patients on the drug tamsulosin hydrochloride, according to an advisory from the American Society of Cataract and Refractive Surgery. The advisory is available at: *http://www.ascrs.org/lists/refractive/2005/doc00004.doc*

Tamsulosin hydrochloride – which is known by such trade names as Flomax® in the United Stated and Omnic® in Europe – is one of the most commonly prescribed agents to improve urinary outflow in men with benign prostatic hypertrophy. In Europe, the drug is marketed by the Japanese-based pharmaceutical firm Yamanouchi.

ASCRS has asked ophthalmologists to submit IFIS complication reports to the ASCRS EyeMail Cataract list serv for analysis. Those not using the EyeMail service are asked to report their experiences to Eye Mail's editor at *mcdonaldje@ mcdonaldeye.com*

"We urge physicians to report their experiences with Flomax® and Omnic® patients and their methods for dealing with intraoperative complications. Doing so will enable us to make recommendations regarding this medication," said the EyeMail editor, J. E. "Jay" McDonald II, MD.

Two studies link agent to syndrome

The ASCRS Advisory followed the report of preliminary results from two companion studies conducted by David F. Chang, MD and John R. Campbell, MD. Those results appeared in the January issue of the ASCRS monthly magazine, EyeWorld. The EyeWorld article is available at: *http://www.eyeworld.org/ article.php?sid=2299.*

The separate prospective and retrospective studies, which together included more than 1,600 cases and 1250 patients, found that IFIS was diagnosed in approximately 2% of cataract patients. There was highly statistically significant evidence that the syndrome was caused by tamsulosin hydrochloride. Dr Chang's and Dr Campbell's findings have been accepted for publication in the Journal of Cataract & Refractive Surgery and will also be reported at the ASCRS Meeting in April in Washington, D.C.

Dr Chang and Dr Campbell found that IFIS was characterised by iris prolapse and billowing, and progressive intra-operative miosis that could not be prevented by sphincterotomies or mechanical pupil stretching. In the retrospective study there was a higher rate of posterior capsule rupture among such patients.

"These are difficult cases, particularly because surgeons previously had no way to anticipate when IFIS would occur," Dr Chang commented. "This was true in our two studies, because the prospective study was masked." Dr Chang advises that for patients on tamsulosin, iris retractors or pupil expansion rings will reliably maintain a large pupil size for surgery. As an alternative, using Healon 5 (Advanced Medical Optics, Inc., Santa Ana, CA) with low flow and vacuum settings can also expand the pupil and block the iris from prolapsing. However, the Healon 5 must be repeatedly re-injected as it is aspirated.

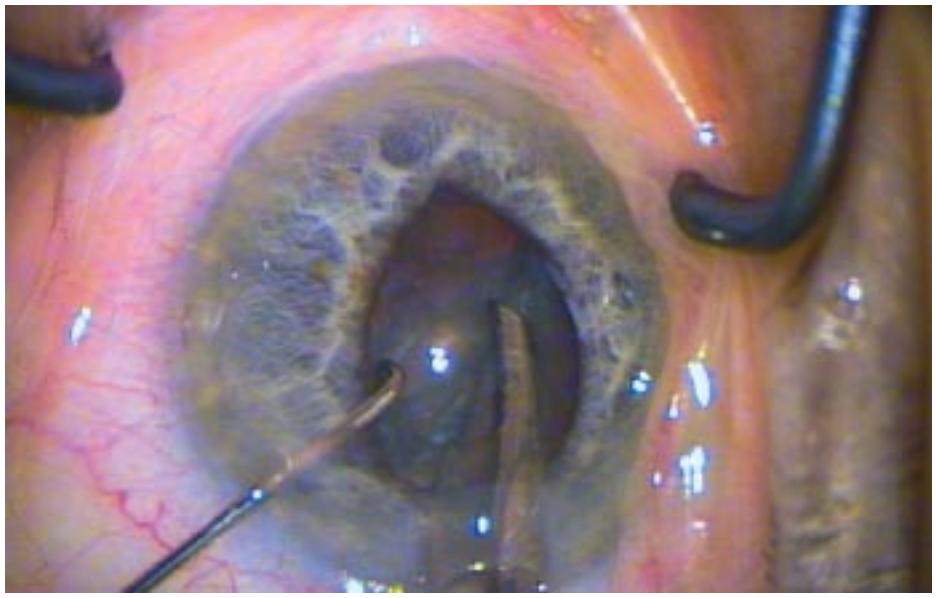
Dr Chang is organising a multicenter trial to prospectively evaluate the outcomes and complication rate of cataract surgery performed in Flomax® patients using one of these three small-pupil techniques. "These are methods that most practicing surgeons would be able to use," said Dr Chang. "While most cataract surgeons have encountered these cases, patients and their urologists won't understand what the significance of a floppy iris is and will question whether the drug is safe to take," he explained. "Now that we can predict when IFIS will occur, this prospective study will evaluate whether these Flomax cases can be safely managed with appropriate techniques."

Soon after ASCRS issued the advisory, ASCRS President Priscilla Arnold, MD, spoke with the President of the American Urological Association, Brendan Fox, MD, to brief him on the concerns relating to the use of tamsulosin hydrochloride.

"I emphasised that we were not suggesting a change in prescribing patterns at this time," Dr Arnold said. "He was very open to what we had learned and expressed his interest in communicating it to the urological community – especially what we learn from the follow-up investigation."

Dr Chang added that the most important thing now is for cataract surgeons worldwide to be educated about IFIS, and its association with tamsulosin.

According to Dr Chang, tamsulosin hydrochloride is a systemic alpha-1 antagonist that relaxes the smooth muscle in the bladder neck and prostate, improving urinary flow in patients with symptomatic benign prostatic hypertrophy (BPH). Other alpha-1 blockers used for BPH included terazosin hydrochloride and doxazosin mesylate. There are three known alpha-1 receptor subtypes – A, B, and D. Tamsulosin is unique in that it is the only subtype-specific drug in this class, being highly selective for the alpha-1A receptor that predominates in the prostate. Dr Chang explained that this makes tamsulosin more uroselective than other alpha-1 blockers for BPH, resulting in a lower incidence of postural hypotension. Dr Chang and Dr Campbell reviewed the pharmacologic literature and discovered that the alpha-1A receptor subtype also mediates contraction of the iris dilator smooth muscle. They postulate that the iris floppiness is due to a loss of the normal iris dilator smooth muscle tone.



Patients receiving the prostate drug tamsulosin hydrochloride may be at an increased risk of developing "floppy iris syndrome", a condition characterised by subnormal preoperative pupil dilation and repeated intraoperative prolapse of a billowing, floppy iris.

Agent may have long term side effects on iris muscles

Surprisingly, IFIS has been seen in several patients who have been off tamsulosin for one to two years, suggesting that there is some semi-permanent loss of dilator muscle tone in these eyes. Dr Chang points out that IFIS has also been reported in women taking tamsulosin for urinary retention symptoms. However, IFIS does not appear to be caused by any of the other alpha-1 blockers that are not sub-type specific.

Since issuing its advisory on IFIS, the executive committee of ASCRS has established a special Flomax® Working Group to further investigate problems associated with tamsulosin hydrochloride during cataract surgery, and to develop recommendations for clinicians based upon further studies. The working group is chaired by EyeMail's Dr McDonald and includes Dr Chang among its members.

Since the formation of the working group, FDA officials have contacted ASCRS seeking additional information on the IFIS syndrome and problems ophthalmologists have encountered with it.

According to ASCRS's Dr Arnold, the association will rely heavily on the outcome of Dr Chang's follow-up study in formulating any recommendations to cataract surgeons about treating patients on tamsulosin.

"We will look to Dr Chang's multicentre study to provide us with sound data from which we will then consider an appropriate course of action with regard to potential recommendations – if appropriate – to ophthalmologists, other physician groups, and the FDA," Dr Arnold said.

No reports of adverse events in Europe

A spokesperson for the London-based European Medicines Evaluation Agency said that the EMEA had received no reports of any complications associated with tamsulosin hydrochloride and cataract surgery. He explained that because tamsulosin hydrochloride was licensed through individual European Union member states – and not centrally through the EMEA – it would be up to the individual national regulatory agencies to monitor reports of complications involving the drug. "They are ones who would have to take any regulatory action on the product," said the EMEA's Martin Harvey-Allchurch. Mr. Harvey-Allchurch added that the European state agency that first approved a drug would usually lead the monitoring of reports of complications.

In the case of tamsulosin hydrochloride, the first European national authority to license it was the Dutch Medicines Evaluation Board which approved it in 1995. A spokesperson for the Dutch Board said that it had received no reports to date about complications arising from tamsulosin hydrochloride use and cataract surgery.

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Pharmaceutical companies decline comment on 'floppy iris' findings

For now, the two pharmaceutical companies that market tamsulosin hydrochloride – the Germany-based Boehringer Ingelheim Pharmaceuticals and the Japan-based Yamanouchi Pharmaceutical Company – are withholding any comment on findings that the drug may cause "Intra-operative Floppy Iris Syndrome."

The syndrome – which is know by the acronym "IFIS" – is characterised by subnormal preoperative pupil dilation and repeated intraoperative prolapse of a billowing, floppy iris in patients on the drug tamsulosin hydrochloride, according to an advisory from the American Society of Cataract and Refractive Surgery.

In a statement to EuroTimes, Boehringer Ingelheim said it was "aware" of the ASCRS advisory. "We are currently investigating these reports and cannot comment further at this time," the company said in its statement.

Boehringer Ingelheim markets the drug in the United States under the trade name of Flomax®.

Yamanouchi, which invented the drug and markets it in Europe under the trade name of Omnic®, issued a similar statement.

In its statement to EuroTimes, Yamanouchi said it had not had "the opportunity to review" the two studies that led to the ASCRS advisory. Findings from those studies, by two American ophthalmic surgeons – David F. Chang, MD and John R. Campbell, MD – appeared in the January issue of the ASCRS monthly magazine, EyeWorld.

"Until Yamanouchi has had the opportunity to fully review the studies we are not in a position to comment," the statement added. "As soon as we have conducted an investigation we will of course take any actions to safeguard patient health and safety if it is needed."

"It is important to note that the authors of this report emphasised that:

1. There is no indication that Flomax® causes any symptoms or problems in eyes that have not been operated upon

2. The authors are not recommending that any Flomax® prescribing practices should be changed. One author stated: 'Rather we want to educate ophthalmologists about this syndrome, so that upon eliciting any history of Flomax® use, they can anticipate IFIS and follow the surgical recommendations from our study.'"

"Yamanouchi will be reviewing the studies and working with the leading experts on any surgical recommendations, which may be necessary to ensure the best outcome for patients."

Cataract surgeons and researchers suggest ways to manage IFIS

Managing Intraoperative Floppy Iris Syndrome (IFIS) begins with careful questioning of patients about drug use, according to two leading American cataract surgeons.

The surgeons, David F. Chang, MD and John R. Campbell, MD, made their comments after two companion studies – one retrospective and one masked prospective - linked the drug tamsulosin hydrochloride to the syndrome. The syndrome is characterised by subnormal preoperative pupil dilation and repeated intraoperative prolapse of a billowing, floppy iris.

The doctors, who reported their findings in the January issue of EyeWorld magazine, urged ophthalmologists to question patients about tamsulosin hydrochloride preoperatively, particularly if the pupil dilates poorly. Tamsulosin hydrochloride is currently the most widely prescribed drug for benign prostatic hypertrophy.

The drug, which comes in an orange and brown capsule, bears the trade name of Flomax® in the United Stated and Omnic® in Europe. In the European Union, the drug is marketed by Yamanouchi Europe BV, a subsidiary of the Japan-based Yamanouchi Pharmaceutical Company. Tamsulosin hydrochloride is usually taken once a day at breakfast-time to help improve urinary outflow by relaxing the smooth muscle in the prostate and bladder neck.

Although stopping the drug for two weeks may reduce the iris floppiness and increase the pupil dilation, it does not completely eliminate the floppy behaviour of the iris, according to the doctors. This finding would suggest that tamsulosin hydrochloride has a long-lasting effect on the iris dilator smooth muscle.

Another important finding is that the most common methods of pupil enlargement – mechanical stretching or partial thickness sphincterotomies – do not maintain adequate pupil dilation in tamsulosin patients. "Iris retractors are an excellent strategy for IFIS," said Dr Chang. "Historically, they have been less popular because they are more costly and time-consuming to use," he explained. "In addition, they are more difficult to insert following completion of the capsulorhexis, which can be inadvertently snagged by the hooks."

"Therefore, the ability to anticipate IFIS allows surgeons to reconsider their usual method of small pupil management in favour of self-retaining pupil expansion devices inserted prior to capsulorhexis initiation," the doctors wrote in their EyeWorld article. Dr Chang recommends placing the iris hooks in a diamond configuration, as reported by Tom Oetting MD (J Cataract Refract Surg. 2002;28:596-598).

Dr Chang also postulated that bimanual microincisional phaco might reduce iris prolapse in IFIS eyes, because of the tighter incisions. "Unfortunately, the iris still managed to prolapse to these incisions in a number of IFIS cases where this was tried," he said.

Optometrists lose right to operate

In a major victory for ophthalmologists, the largest health service in the United States has banned optometrists from performing refractive surgery procedures.

The Veterans Health Administration – which is responsible for treating millions of retired soldiers and their families – has adopted new regulations directing that only ophthalmologists will be allowed to perform therapeutic laser procedures in its medical facilities.

With the new regulations, the Veterans Health Administration reversed a previous directive that optometrists could perform procedures such as PRK under the supervision of an ophthalmologist.

Details about the previous regulations – which provoked a national campaign – appeared in the October, 2004 issue of EuroTimes. The issue arose because the Veterans Health Administration allowed any practitioner to practice to the full extent or his or her state license.

Under the law of one American state – Oklahoma – optometrists are licensed to perform such laser-based procedures as capsulotomy, laser trabeculoplasty, peripheral iridotomy, PRK, and LASEK. Oklahoma is the only state in the United States that licenses optometrists to practice laser surgery.

The American Society of Cataract and Refractive Surgery and the American Academy of Ophthalmology, which led the campaign to change the Veterans Health Administration regulations, welcomed the decision as a victory for patient care.

"Patient safety is paramount," said Priscilla Arnold, MD, President of ASCRS.

"The position of state and federal regulatory authorities has been to restrict the performance of surgery to doctors. Specific surgical training is mandatory for such privileges."

"Ophthalmic surgery should be guarded by the same consideration for public safety, and be performed only by those professionals who have been properly trained are licensed to perform surgery," Dr Arnold added.

Although fewer than 20 optometrists had the right to perform laser surgery rights within Veterans Health Administration hospitals, ophthalmologists were worried that if they did not oppose the practise, more optometrists would enter the operating theatre to perform increasingly complex procedures for which they did not possess the appropriate education and training. The Veterans Health Administration is the largest provider of medical care in the United States. Some 26 million ex-servicemen and ex-servicewomen – and another 40 million of their family members – are eligible for treatment at more than 1,000 hospitals and clinics throughout the United States.

In addition to pressure from physician groups, the Veterans Health Administration was unable to persuade a working group of ophthalmologists, optometrists, and administration officials to agree to details about how ophthalmologists could supervise optometrists performing laser procedures.

Anthony Principi, who heads the Veterans Health Administration as Secretary of Veterans Affairs, acknowledged he implemented the new regulations banning optometrists from performing laser surgery because of concerns of physicians and the inability of the working group to develop a plan to implement the regulations.

Mr. Principi's comments appeared in a letter to U.S. Representative John Sullivan, who had proposed a special national law that would have prohibited optometrists from performing eye surgery in any clinic or hospital owned by the Veterans Health Administration.