Intraoperative Floppy Iris Syndrome: Possible Relationship with Alpha-1 Adrenergic Receptor Antagonists

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Intraoperative floppy iris syndrome involves a clinical triad of pupil constriction, fluttering and billowing of the iris stroma, and propensity for iris prolapse during cataract surgery [1]. IFIS is clinically significant because of the danger that it may compromise the safety and effectiveness of cataract surgery. Without adequate pupil dilation, IFIS may reduce visualization of the surgical field, including the cataract itself. This impairs removal and can lead to other complications such as rupture of the posterior capsule, which further increases the risk of other vision-threatening complications of cataract surgery [2].

Benign prostatic hyperplasia is a common urological disorder in older men. BPH increases the risk of complications such as urinary retention, recurrent urinary tract infections, and urinary incontinence [3,4]. The most common medication treatment options for BPH are divided into two therapeutic classes. The 5-alpha reductase inhibitors finasteride and dutasteride reduce prostate size by inhibiting conversion of testosterone to dihydrotesterone. Although generally well tolerated, 5ARI are associated with sexual side effects, and therapeutic trials require several months of therapy [5]. Alpha-1 adrenergic receptor antagonists – such as terazosin, doxazosin, alfuzosin, and tamsulosin – reduce bladder outlet obstruction by relaxing prostate smooth muscle tissue surrounding the urethra and have comparable effects in symptom reduction [6]. Originally developed as an antihypertensive medication, terazosin and doxazosin have the potential for serious adverse effects such as orthostatic hypotension and syncope [7]. For these reasons newer uroselective agents have been developed – including tamsulosin and alfuzosin. Tamsulosin, the first α1A adrenergic receptor antagonist, reduces the risk for orthostatic side effects relative to non-selective agents. Although alfuzosin is not specific for α-receptor subtypes, it also exhibits lower rates of orthostatic effects relative to older agents, possibly due to its extended-release formulation which prevents peaks in serum concentrations.

Cataracts are opacities within the natural crystalline lens of the eye that can result in impaired vision and possibly blindness in advanced stages. Since age is the predominant risk factor for both BPH and cataracts, physicians can expect to see increasing numbers of patients on α1AR antagonists who require operative intervention for cataract removal. However, patients taking α1AR antagonists may be at risk for IFIS during cataract surgery.

The relationship between α1AR antagonists and IFIS was originally reported in a retrospective chart review of 511 patients undergoing cataract surgery [1]. Twenty-seven patients (5.3%) totaling 40 eyes had preoperative exposure to α1AR antagonists. Ten of 16 patients taking tamsulosin prior to surgery developed IFIS. In the remaining 11 patients on other α1AR antagonists, there were no documented cases of IFIS. However, all 27 patients had "poor or moderately poor dilation." In the prospective series, 900 consecutive cataract surgeries were performed in 741 patients, and IFIS was observed in 16 patients (2.2%), including 14 who had documented concomitant use of tamsulosin [1]. Of the two remaining patients, one had discontinued tamsulosin 3 years prior to surgery and one had no history of tamsulosin exposure. IFIS was reported in both eyes of the five patients taking tamsulosin who required bilateral cataract surgery. Despite the authors' initial identification of a potentially serious complication of cataract surgery, reported limitations of the study include lack of covariate data and the modest reported use of α1AR antagonists [2]. Patient-specific data including co-morbid disease states and concomitant medications were not reported, which could have identified specific confounding variables. Furthermore, some have suggested that tamsulosin use may have been underreported as it was only documented in 1.9% of patients despite being a widely prescribed agent for treatment of BPH in a population with a historically high prevalence of this condition

IFIS = intraoperative floppy iris syndrome
BPH = benign prostatic hyperplasia
5ARI = 5-alpha reductase inhibitors

α1AR = alpha-1 adrenergic receptor

(the mean ± standard deviation age of tamsulosin-treated patients was 76.6 ± 8.8 years). It should be noted, however, that diagnosis of BPH does not always require pharmacological treatment, specifically in patients with mild American Urological Association symptom scores [8]. This may partially explain the relatively low percentage of tamsulosin use in a population with a high probability of BPH. Furthermore, a retrospective study spanning more than 5 years demonstrated that among Canadian men the prevalence of any α1AR antagonist use prior to cataract surgery was 5% [9]. Thus, it is reasonable to assume that the 1.9% reported use of tamsulosin in the original report may actually approximate the true value.

In the most recent study assessing incidence, IFIS was reported to be 1.6% among 774 patients [10]. IFIS was documented in 14 of 18 patients (77.8%) taking tamsulosin and, consistent with the original report by Chang and Campbell [1], tamsulosin use overall was observed in 2.2% of patients. The duration of tamsulosin use, although increased among patients diagnosed with IFIS, was not statistically significant compared to those without IFIS.

Following the original report suggesting a stronger link between tamsulosin and IFIS relative to other α1AR antagonists, subsequent case reports of IFIS have been published of men taking other agents including alfuzosin, doxazosin, and terazosin [11-14]. Furthermore, saw palmetto (*Serona repens*), a widely used alternative therapy for BPH, was also associated with IFIS in two patients [15]. Neither of the patients had taken prescription medications for BPH and they developed moderate IFIS during cataract surgery. Despite the development of IFIS, the authors reported no significant surgical complications. Of note, other medications that could potentially predispose patients to IFIS were not reported by the authors. Finally, two cases of IFIS were associated with finasteride intake [16]. Neither patient had taken systemic α1AR antagonists prior to surgery, and, to date, these are the only published cases associated with 5-alpha reductase inhibitor therapy.

A recent study directly compared the incidence of IFIS attributable to tamsulosin with an active comparator group [17]. In this retrospective study of 64 men totaling 92 eyes, there was an increased risk of IFIS in patients exposed to tamsulosin (86.4%) when compared to alfuzosin (15.4%). The adjusted odds ratio for IFIS in patients taking tamsulosin when compared to alfuzosin was 32.15 (95% confidence interval 2.74–377.41). Furthermore, a fivefold increase in surgical complication rates was observed in patients diagnosed with IFIS, highlighting its clinical significance. In contrast to the original study that first identified IFIS, covariate analyses to determine risk attributable to other disease states were conducted.

Currently, the risk of IFIS has only been demonstrated with systemic use of α1AR antagonists. In a study comparing the incidence of IFIS between topical and systemic use of α1AR antagonists, no cases were observed in patients taking bunazosin, a topical non-selective α1AR antagonist [18]. In the tamsulosin comparator group, the incidence of IFIS was 1.1%. Interestingly, the results may have differed had the topical agent used also been specific for the α1AAR subtype.

In response to multiple reports of an increased risk of IFIS, the package labeling of tamsulosin and other α1AR antagonists has been updated to reflect this potential risk. The labeling further acknowledges that the benefits of stopping an α1AR antagonist prior to cataract surgery remains unknown (package insert: Flomax®, Boehringer Ingelheim).

The most comprehensive review of adrenergic receptors in relation to the potential pathophysiology of IFIS was recently published [9]. Contraction of the iris dilator muscle via adrenergic stimulation results in mydriasis (dilation), which is necessary during cataract surgery. Hence, agents such as topical phenylephrine, an α1AR agonist, are routinely used in cataract surgery. Besides the effects of α1AAR on prostate tissue, several animal studies have isolated the α1AAR subtype as the mediator of iris smooth muscle dilation [3]. It has been postulated that since tamsulosin is the only specific α1AAR antagonist marketed for BPH, it may also inhibit α1A receptors in the iris, thereby leading to IFIS. Although not specific to the α1A receptor, agents such as terazosin and doxazosin act at these receptors as well. The pathophysiology may be considerably more complex as case reports of IFIS have been linked to other medications including chlorpromazine, labetolol and donepezil, which have three distinct mechanisms of action [19-21].

In this issue of the journal, Leibovici et al. [22] describe the association between tamsulosin and intraoperative floppy iris syndrome. They concluded that an association between preoperative treatment with tamsulosin and IFIS is probable. This observation deserves further research to establish causality. Meanwhile, it seems prudent to perform an ophthalmic examination prior to prescribing tamsulosin. In addition, family physicians are the most accessible of the health care providers, providing many opportunities to discuss these risks with patients when they present for new prescriptions or refills for tamsulosin or other α1AR antagonists. Furthermore, if cataract surgery is planned in the near future, patients and providers may choose to delay medical treatment for BPH until after surgery. The severity of symptoms and the risk of BPH-related complications such as acute

urinary retention should be considered against the potential complications during cataract surgery. It is important that patients and providers make an educated decision on this matter. While there is still much to elucidate about the relationship between α1AR antagonists and IFIS, family physicians should be knowledgeable about these emerging risks as well as their clinical significance when counseling patients.

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