Selecting an Appropriate α1-Adrenoceptor Blocker in the Treatment of Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

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INTRODUCTION

With increases in life expectancy because of advances in medical care, the aging of the population has become an important issue worldwide. In men, the prevalence of benign prostatic hyperplasia (BPH) has constitutionally increased with aging and has had an increasing impact on medical care [1]. Prior to the 1980s, surgical management such as transurethral resection of the prostate (TURP) was the only management available for BPH other than watchful waiting and conservative management. The use of TURP and other surgical procedures has declined rapidly since the 1990s with the introduction of medical therapies such as α1-adrenoceptor (α1-AR) blockers and 5α-reductase inhibitors for lower urinary tract symptoms associated with BPH (LUTS/BPH) [2,3]. Because of their rapid and sustained relief of symptoms irrespective of prostate size and the aging process, α1-AR blockers have become the preferred medication for patients with LUTS/BPH [4]. However, one of the more frustrating questions for physicians is which α1-AR blocker is best. Treatment with good efficacy/tolerability, a good benefit/risk ratio, and reasonable costs which improves quality of life will be more acceptable to patients and physicians [5]. These all need to be balanced against the extent to which patients are bothered by urinary symptoms and how these affect their daily living and their partners. This article explores these questions and the various α1-AR blocker treatment options for LUTS/BPH.

RATIONALE FOR USING α1-AR BLOCKERS

BPH is a nonmalignant proliferation of both the stromal and epithelial cells of the prostate gland. It arises in the periurethral and transition zones of the prostate and is an inescapable phenomenon for the aging male population [6,7]. By the age of 80 years, approximately 90% of men develop BPH [1]. Static and dynamic factors contribute to the pathophysiology of bladder outlet obstruction in men with BPH [6,7], which can result in bothersome LUTS and impair quality of life [8]. Static obstruction is due to bulk enlargement of the prostate encroaching on the prostatic urethra and bladder outlet, and dynamic obstruction is related to the tension of prostate smooth muscle [6,7]. The increased smooth muscle tone seen in BPH is related to copious adrenergic innervation of the prostate capsule and bladder base. These regions contain an abundant population of α1-ARs, which is further increased in BPH [6,7]. Three subtypes of α1-AR (α1a, α1b and α1d) have been cloned and pharmacologically characterized [7,9]. The α1a subtype is seen as the primary regulator of smooth muscle tone in the bladder neck and prostate. In contrast, the α1b subtype regulates blood pressure via arterial smooth muscle relaxation and presents to a lesser degree in the detrusor muscle, while the α1d subtype is associated with contraction of the detrusor muscle as well as sacral spinal cord innervation [2,7]. In 1976, Caine et al first reported the effectiveness of α-AR blockers in the treatment of LUTS/BPH [10]. Over the last 30 years, a number of α1-AR blockers have been approved for the treatment of LUTS/BPH. Terazosin, doxazosin (also available as doxazosin gastrointestinal therapeutic system [GITS]), alfuzosin and tamsulosin are the four most frequently prescribed α1-AR blockers worldwide, and more than 20 randomized clinical trials have consistently demonstrated their safety and efficacy [11-14].

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EFFICACY OF α1-AR BLOCKERS

In 1999, Djavan and Marberger first performed a meta-analysis on the efficacy of four α1-AR blockers (terazosin, doxazosin, alfuzosin and tamsulosin) in patients with LUTS/BPH [11]. They analyzed clinical placebo-controlled or direct comparative studies derived from a MEDLINE search and found all four α1-AR blockers when administered at their full therapeutic dose produced comparable improvements in symptoms and urinary flow. Total symptom scores in general improved by 30%-40% and the maximal uroflow rate (Qmax), by 16%-25% [11]. Subsequently, meta-analyzed data from the American Urological Association in 2003 also suggested that these four α1-AR blockers were similarly effective in relieving symptoms, producing on average a 4-to-6 point improvement in symptom scores and a 2-to-4 point decrease versus a placebo [12]. The four α1-AR blockers also provided equivalent benefits in improving the Qmax and quality of life [12].

In a further update analysis from Djavan and coworkers with included new formulations of α1-AR blockers (eg, alfuzosin prolonged release [XL] and doxazosin GITS), all studied α1-AR blockers had comparable efficacy in improving symptoms and the Qmax when administered at their full therapeutic dose [13]. Those α1-AR blockers that required dose titration and were initiated at subtherapeutic doses (eg, terazosin) had slower onsets of action than other α1-AR blockers that could be initiated at a full therapeutic dose (eg, tamsulosin) [13]. Recently, Nickle et al performed another meta-analysis to evaluate the efficacy of α1-AR blockers currently prescribed for LUTS/BPH [14]. They analyzed double-blinded, prospective, placebo-controlled trials

from a literature review, and found no differences in improvement of symptom scores and Qmax among different α_1-AR blockers compared with placebo [14]. In conclusion, although some α_1-AR blockers like terazosin and doxazosin require titration to therapeutic levels, all α_1-AR blockers seem to have similar efficacy in improving symptoms and flow [11-14].

SAFETY AND TOLERABILITY OF α_1-AR BLOCKERS

Because all α_1-AR blockers seem to have similar efficacy in the treatment of LUTS/BPH, it is important to take the different side effects into consideration when choosing an appropriate α_1-AR blocker. The four currently prescribed α_1-AR blockers vary in their subtype selectivity and are associated with different side effect profiles [7]. Because α_1-AR blockers can cause vasodilation and associated vascular adverse events (eg. dizziness, hypotension or syncope) which can be life threatening, clinicians should take care when treating elderly patients [14]. In the meta-analysis from Djavan et al, alfuzosin and tamsulosin appeared to be better tolerated than terazosin and doxazosin. In addition, they found tamsulosin had less effect on blood pressure than alfuzosin, especially in elderly patients [11,13]. These results were also reported in a review from Milani et al [15].

Terazosin and doxazosin, originally developed as antihypertensive drugs, are non-subtype-selective α_1-AR blockers. Both are reported to be associated with an increased risk of hypotension and dizziness when used at therapeutic levels, and thus require titration to reduce the risk of vasodilatory side effects [16,17]. Alfuzosin is also a non-subtype-selective α_1-AR blocker, but is considered uroselective and is associated with fewer vasodilatory adverse events [7,18]. Tamsulosin differs from other α_1-AR blockers in that it is selective for α_{1a} and α_{1d} subtypes, so it is associated with a low incidence of vasodilatory side effects [7,19]. Both alfuzosin and tamsulosin do not require titration [7]. In humans, both α_{1a}-ARs and α_{1b}-ARs regulate blood pressure and peripheral vascular resistance, and the relative proportion of α_{1b}-ARs to α_{1a}-ARs increases with age, so α_{1b}-ARs are more dominant in the peripheral vasculature and exert more influence on blood pressure in the elderly population [20]. The absence of affinity for the α_{1b}-ARs shown by tamsolosin may explain why it had a lower incidence of vasodilatory side effects than other agents in clinical trials [7].

Doxazosin GITS is a new controlled release formulation of doxazosin that is designed to reduce the peak-to-through ratio, minimizing the need for titration and vasodilatory adverse events [21,22]. In a recent meta-analysis from Nickel et al, all non-subtype-selective α_1-AR blockers including doxazosin GITS still showed a statistically significant increased risk of vascular-related adverse events compared with a placebo. Tamsulosin, a subtype-selective α_1-AR blocker, showed an increased risk but it was not statistically significant compared with a placebo [14].

SEXUAL ISSUES WITH α_1-AR BLOCKERS

In addition to vascular-related adverse events, α_1-AR blockers are associated with other kinds of adverse events especially related to sexual function. This may be an important factor used to determine which α_1-AR blocker treatment is optimal, particularly for younger, sexually active men with BPH.

Tamsulosin is associated with a low but statistically significant increased risk for abnormal ejaculation compared with a placebo [12, 13]. Most studies have observed no significant increase in the risk of ejaculation disorder with alfuzosin [23,24], and one comparative study showed no significant difference between tamsulosin and alfuzosin for risk of abnormal ejaculation [25]. In an attempt to elucidate the mechanism by which α_1-AR blockers might cause ejaculation disorder, Hellstrom and coworkers used a randomized, three-way crossover design, comparing the effects of 5 days of treatment with 0.8 mg tamsulosin daily, 10 mg alfuzosin daily and a placebo on ejaculation in healthy adult men [26]. In the subjects on tamsulosin, 89.6% had a decrease in ejaculated volume and 35.4% had a complete lack of ejaculation (anejaculation). In contrast, there was no reported anejaculation in any subjects in the alfuzosin or placebo groups. The ejaculatory disorders with tamsulosin were not attributed to retrograde ejaculation. Other mechanisms such as peripheral and/or central effects of tamsulosin may be involved [26]. Although abnormal ejaculation is more common in patients using tamsulosin than other α_1-AR blockers, less than 1% of patients reporting abnormal ejaculation in placebo-controlled trials discontinued treatment because of it, and patients who reported abnormal ejaculation remained in clinical trials longer than those not reporting this adverse event [15].

None of four currently available α_1-AR blockers demonstrated a deleterious effect on erectile function compared to a placebo [12]. In contrast, it has been implied that all α_1-AR blockers slightly improve overall sexual function [13]. Much epidemiologic and clinical research has demonstrated that LUTS/BPH and ED in aging males are strongly linked and may share common pathways [27-29]. One proposed common pathway between LUTS/BPH and ED is α_1-AR imbalance [28]. Various subtypes of α_1-ARs have been identified in the penile tissue, and α_{1a} and α_{1d} receptors are reported to be the predominant α_1-AR subtypes in the penile corpus cavernosum [28]. Recently, several basic science and clinical studies have demonstrated a beneficial effect on sexual function when using α_1-AR blockers for LUTS/BPH [28,30]. In clinical studies, alfuzosin [31,32], doxazosin (doxazosin standard and doxazosin GITS) [33,34], and tamsulosin [35] have been reported to improve erectile function. The Treatment of Mild Hypertension Study also documented that patients receiving doxazosin reported a lower incidence of ED than patients taking other antihypertensive agents (acebutolol, amlodipine, chlorthalidone and enalapril) [36].

Phosphodiesterase type 5 (PDE-5) inhibitors are currently commonly used for the treatment of ED. In men with ED, adding α_1-AR blockers to PDE-5 inhibitors has been reported to improve erectile function more than using PDE-5 inhibitors alone [37-40]. However, this combination must be used with caution because of the vasodilatory adverse events associated with both classes of drugs [30]. Sildenafil given with doxazosin and vardenafil given with terazosin have been reported to evoke orthostatic hypotension in some patients [30]. One study showed that tadalafil at normal doses (20 mg) increased the hypotensive effect of doxazosin, but little or no hemodynamic interaction was found with tamsulosin [41]. Another study also found that tadalafil showed no clinically relevant hemodynamic interaction in patients using alfuzosin daily [42]. A combination of vardenafil and doxazosin, resulted in no symptomatic hemodynamic effects in a recent study [43]. In men who have been on long-term therapy with α_1-AR blockers, the effect of PDE5 inhibitors on blood pressure might be less significant [44].

In conclusion, all α_1-AR blockers have a similar efficacy in the treatment of LUTS/BPH, but they differ in their potential to induce related adverse events such as vasodilatory side effects and sexual dysfunction. In elderly men and those with cardiovascular comorbidity or comedication, tamsulosin may be optimal because it is well tolerated and results in fewer adverse vascular-related events than other α_1-AR blockers. But in younger sexually active men with BPH, tamsulosin should be used with caution because of a higher incidence of abnormal ejaculation.

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