Medication Use and Safety Issues Associated with Male Lower Urinary Tract Symptom Treatment

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ABSTRACT

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are common and a significant cause of morbidity in ageing men. The α-adrenoceptor (AR) antagonists are documented to be beneficial for the treatment of benign prostatic obstruction, to improve the patient's quality of life and to reduce the necessity of surgical intervention. 5α-reductase inhibitors are also well-established effective agents for the relief of LUTS/BPH and are able, to shrink the prostate volume and resolve prostate-related bleeding. However, an overactive bladder, which is characterized by urge, frequency, urge incontinence, and nocturia, might persist even after the surgical removal of the obstruction. Many studies have confirmed the effectiveness of antimuscarinics on the overactive bladder. In this review, we summarize and discuss recent evidence on the efficacy and safety of these treatment modalities when used for male LUTS/BPH.

Keywords: benign prostatic hyperplasia, lower urinary tract symptoms, overactive bladder, antimuscarinics, safety

INTRODUCTION

Lower urinary tract symptoms (LUTS) are any combination of urinary symptoms, including voiding symptoms (hesitancy, weak stream, intermittency, terminal dribbling, and feeling of incomplete emptying) and storage symptoms (frequency, urgency, and nocturia). In the male population, LUTS are generally attributed to benign prostatic hyperplasia (BPH) and are significant factor in morbidity among ageing men. Historically, endoscopic prostatectomy had been the standard treatment and has provided a most effective solution for LUTS/BPH. Nonetheless, in the past two decades, the α-adrenoceptor (AR) antagonists have been documented to be beneficial for treatment of benign prostatic obstruction and have been found to be able, to improve the quality of life of these patients as well as reducing the necessity of surgical intervention. 5α-reductase inhibitors are also well-established as effective agents in the relief of LUTS/BPH. In addition, they are able to shrink the prostate volume and to resolve prostate-related bleeding. Furthermore, recent studies have confirmed the effectiveness of antimuscarinic agents in the treatment of storage symptoms in males with BPH. However, the guidelines published by American Urological Association (AUA) and European Association of Urology (EAU) do not include antimuscarinic agents as a recommended treatment of choice for men with BPH (Fig. 1). In this review, we discuss the efficacy and safety of these abovementioned main medications for LUTS/BPH in men.

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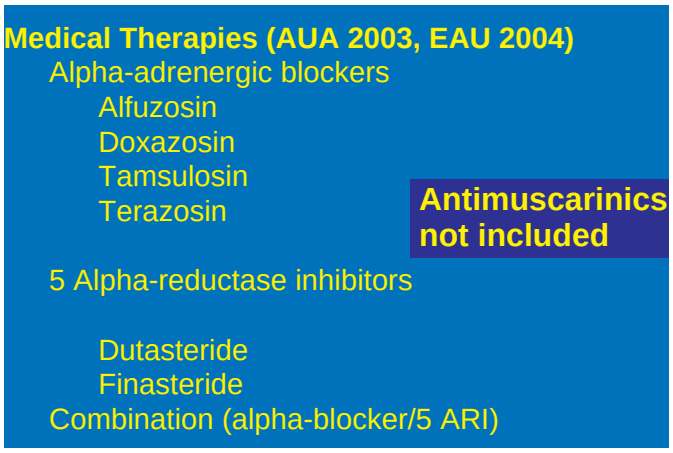

Fig. 1. Medications recommended for male LUTS/BPH by guidelines.

ALPHA-ADRENERGIC ANTAGONISTS

BPH with LUTS has been proposed to arise by two major mechanisms, namely static and dynamic components; specifically, these are direct bladder outlet obstruction (BOO) by an enlarged prostate and increased smooth muscle tone resulting in resistance at the prostatic urethra, respectively. The prostate gland contains high levels of both alpha-1 and alpha-2-adrenergicreceptors (ARs) [1-3]. Previous animal studies have demonstrated that alpha AR is the mediator of prostate smooth-muscle contraction. Lepor et al also found that both the alpha 1 and alpha 2 adrenoceptors are present in the human prostate [4]. Taken together, it is believed that the alpha 1 adrenoceptor subtype is the one that mediates prostate muscle contraction ninety-eight percent of alpha-1-ARs are associated with the stromal elements of the prostate and increased prostatic smooth muscle tone [2]. Activation of these receptors will result in impaired flow of urine. However, alpha-ARs are not unique to the prostate. Nonetheless, based on published large scale randomized controlled studies, pharmacological therapies have been the most common modalities prescribed by urologists [5].

In this context, the prostate contains glandular and stromal tissue, which consists of smooth muscle; these form the dynamic component of BOO. Blockade of the α-receptors in the bladder neck cause muscle relaxation and relieve the BOO through inhibiting the sympathetic nervous system-mediated contraction of smooth muscles in the prostatic

tissues [6]. At present, there are four alpha-blockers available, namely doxazosin, terazosin, tamsulosin and alfuzosin that are recommended for patients who have moderate to severe symptoms (IPSS ≥8), according the AUA Guideline Committee. These four alpha-blockers are equally effective and result in an average 4- to 6-point improvement in the IPSS [7]. Such a reduction in the outlet resistance leads to changes in bladder function because α-blockers increase the maximal urinary flow rate (Qmax) and improve both voiding and storage symptoms.

Terazosin is an alpha-1-selective antagonist with a relatively long half-life. The Hytrin Community Assessment Trial demonstrated the effectiveness of this medication [8]. In this study, 2,084 men, who were aged 55 years or older and had moderate to severe urinary symptoms, were randomized to receive treatment with either terazosin or placebo. Terazosin was significantly superior to placebo for all efficacy measures, including the American Urological Association International Prostate Symptom Score (AUA-IPSS), and Qmax. Terazosin is thus an effective medical treatment for male LUTS and BPH.

Doxazosin is also a long-acting, alpha-1-selective antagonist. Several published clinical trials in men with symptomatic BPH, it was demonstrated that doxazosin can dose-dependently increase Qmax by 23% to 28% and decrease symptom scores by 16.4% compared to 9.8% for the placebo group [9,10]. Furthermore, Chapple et al demonstrated that doxazosin can also improve storage symptoms such as frequency, urgency and nocturia after 12-week treatment period [11]. The side-effect profile of this drug has also been shown to be dose dependent. To minimize the frequency of side effects (such as postural hypotension and syncope), doxazosin is typically initiated at a dose of 1 mg that is administered once daily. Hernandez et al [12] conducted an open-label, non-controlled, observational surveillance study, which recruited 3,684 men with BPH; these men received 4 to 8 mg of controlled-release doxazosin gastrointestinal therapeutic system (GITS) for 6 months. The results indicated that the hypotensive effect was much smaller in normotensive subjects than in those with hypertension. The authors concluded that this controlled-release formulation of doxazosin was well tolerated and also improved patients' lipid profiles. A Korean open-label, multicenter, uncontrolled, flexible-dose study, which enrolled 475 men with clinical evidence of BPH [13], also showed that treatment with doxazosin GITS for 12 months resulted in a significantly better symptom score, improved real flow rate and better post-void residual urine volume (PVR). In hypertensive patients, treatment with doxazosin GITS was associated with a significant reduction in SBP and DBP. The occurrence rate for postural hypotension was as low as 0.4%.

Alfuzosin, another long-acting alpha-1-adrenoreceptor antagonist, has been shown to improve LUTS and increase urine flow rates with an efficacy similar to that of the above mentioned alpha-1-adrenoreceptor antagonists [14-16]. Furthermore, clinical trials of Alfuzosin have demonstrated that the incidence of cardiovascular side effects is lower than those of terazosin and doxazosin [8,9,14-17]. The mechanistic origin of the reduction in cardiovascular effects remains unclear, however, postulated mechanisms included decreased blood brain barrier penetration, specific distribution to the prostate, and pharmacokinetic differences.

Tamsulosin, which is recommended by the AUA guideline for treatment of men with BPH, is a long-acting alpha-blocker that has greater specificity for the alpha-1A-adrenoreceptor than the alpha-1B-adrenoreceptor. Previous clinical studies have suggested that tamsulosin provides relatively rapid symptom improvement as well as improvement to the Qmax [18]. Long-term studies (up to 60 weeks) have shown that its beneficial effects are sustained over time, as measured by Qmax and symptoms score [19]. The most common adverse effects reported with tamsulosin use are dizziness and retrograde ejaculation. Clinical studies have also demonstrated that tamsulosin can be co-administered with antihypertensives medications such as nifedipine, enalapril, and atenolol without any increased risk of cardiovascular events [20,21].

5-ALPHA-REDUCATSE INHIBITORS (5-ARI)

The 5-ARI drugs (finasteride and the dual inhibitor, dutasteride) are able to ablate the accumulation of intraprostatic dihydrotestosterone (DHT), the hormone most responsible for prostate growth and maintenance. The Proscar Long-Term Efficacy and Safety Study (PLESS) trial [22], a double-blind, placebo-controlled, multicenter study that recruited 3,040 men with moderate to severe LUTS. These men were randomized into a finasteride group(5 mg/day) and a placebo group for the course of the 4-year trial. The results demonstrated that the finasteride group showed a 57% risk reduction for the development of acute urinary retention (AUR) and a 55% risk reduction in the need for BPH related surgery compared with the placebo group. The 4-year Combination of Avodart and Tamsulosin (CombAT) study [23], a multicenter, randomized, double-blind, parallel-group study involving 4,844 men, was reported recently and this also provided data on the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH. This trial supported the efficacy of dutasteride. Adverse effects with finasteride and dutasteride are relatively infrequently reported. The most common side effects are impotence, loss of libido, ejaculatory dysfunction, and gynecomastia.

ANTIMUSCARINICS

Overactive bladder (OAB) can arise in men with BOO and is caused by the BPH and OAB symptoms that are components of LUTS. The application of antimuscarinics is one treatment option for patients with OAB symptoms. Antimuscarinics selectively block the muscarinic receptors associated with the detrusor muscle, which is stimulated by acetylcholine released on activation of the parasympathetic nerves. Consequently, these agents reduce bladder contraction. There are several antimuscarinics available for the treatment of OAB symptoms. However, in this context, tolterodine has a well-documented effect when treating the storage symptoms components of LUTS/BPH. This drug is well tolerated and is the first-line therapy at present. Abrams et al [24] evaluated 221 men with urodynamically confirmed BOO and detrusor overactivity (DO) in a multicentre, randomized, placebo controlled trial aimed at testing the efficacy of tolterodine. After 12 weeks, the patients who received tolterodine exhibited a statistically significant increase in volume to first detrusor contraction as well as maximum cystometric capacity. Although there were statistically significant reductions in bladder contractility index and voiding efficiency as well as an increase in PVR in the tolterodine group, these differences were not statistically or clinically significant. Changes in Qmax were statistically equivalent between the tolterodine and placebo groups. There was only one case of AUR in the placebo group. The incidence of adverse events was similar between the groups, although a dry mouth was

more common in the tolterodine group. Athanasopoulos et al [25] evaluated 50 men with urodynamically diagnosed BOO and DO who were randomly assigned to receive either tamsulosin 400 mg or tamsulosin in combination with tolterodine 2 mg twice daily. After 12 weeks, both groups experienced similar increases in Qmax and reductions in PVR. Patients receiving the combination therapy were found to have a significant reduction in maximum detrusor pressure during micturition and maximum unstable contraction pressure, as well as a significant increase in the volume to first detrusor contraction. Lee et al [26] investigated men with urodynamically confirmed benign prostate obstruction (BPO) only or urodynamically confirmed BPO and DO. These subjects were treated with doxazosin 2 mg for 12 weeks. Any men who did not show an improvement were then treated with doxazosin along with tolterodine immediate release 2 mg twice daily for 8 weeks. Among the men with BPO only, symptom improvement was observed in 79% of patients after 12 weeks of treatment with doxazosin. The addition of tolterodine improved symptoms in 38% of the 16 men with BOO only, who had shown no improvement after treatment with doxazosin alone. In the patients with DO as well as BOO, the symptoms improved only in 35% of them after the initial 12 weeks of treatment with doxazosin. The addition of tolterodine for 8 weeks improved the symptoms in 73% of the 44 men with DO and BOO, who had shown no improvement after treatment with doxazosin alone. Two men treated with tolterodine and doxazosin developed AUR that required catheterization [26]. Kaplan et al [27] conducted a randomized, double-blind, placebo-controlled trial and reported that the men who receive a combination of tolterodine and tamsulosin showed better symptom control and an improved quality of life relative to the men treated with either one of the medications alone or a placebo. A meta-analysis reported by Blake-James et al [28] combined information on adverse events from several randomized controlled trials on different types of antimuscarinics. AUR was an uncommon event and was found to have a comparable incidence for the intervention (0.8%) and control groups (0.6%). The more commonly reported adverse effects were cases of increased difficulty with voiding and substantially increased PVRs (24 patients; 4.9%); these effects resulted in treatment withdrawal from the trials of 14 patients. The most common side effect was dry mouth, which occurred in 14.7% of patients who receiving antimuscarinics as compared with 3.7% of those in the control groups. Taken together, the investigators suggest that when men have very bothersome frequency, urgency, or urge incontinence bladder symptoms, then urologists should consider using a combination of medications for both the bladder and prostate. Given the low complication rate, the prescription of antimuscarinics for men with LUTS and/or BPH is safe and well tolerated. Taken together, the results suggest that clinically meaningful improvements can be achieved by addition of an antimuscarinic therapy in men with persistent storage symptoms; however, there is no true consensus or hard guideline on this. Particularly there is a lack of a cut-off value for Qmax or PVR that can be used to identify when the use of antimuscarinic agents is contra-indicated.

CONCLUSIONS

Treatment of male LUTS should be aimed at relieving bothersome symptoms, improving the patient's quality of life and reducing the disease progression rate. There are many treatment options, including medical, phytotherapy, and surgery; however, in recent years, medical therapy has become the mainstay first-line treatment of choice. Both alpha-adrenergic blockers and 5-alpha-reductase inhibitors are effective and safe. Evidence supporting the role of antimuscarinic agents in men with LUTS and/or OAB symptoms is increasing and supports the efficacy and safety of the use of antimuscarinics.

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