Safety and Efficacy of Addition of an Alpha-blocker to Anti-muscarinic Treatment in Patients with Overactive Bladder

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INTRODUCTION

Lower urinary tract symptoms (LUTS) include storage symptoms, e.g. urgency, frequency, nocturia, and urinary incontinence (UI), and voiding symptoms, e.g. slow stream, intermittent stream, hesitancy, straining, and terminal dribbling [1]. Traditionally, male LUTS are attributed to benign prostate hypertrophy (BPH)/bladder outlet obstruction (BOO), while female LUTS are attributed to overactive bladder syndrome (OAB)/detrusor overactivity (DO). However, the recent EPIC epidemiological study that used 2002 International Continence Society (ICS) definitions of LUTS demonstrated that the prevalence of storage LUTS (men 51.3%; women 59.2%) was greater than that for voiding (men 25.7%; women 19.5%) and postmicturition (men 16.9%; women 14.2%) symptoms combined. The overall prevalence of OAB was 11.8%; the prevalence rates were similar in men and women aged ≥18 years and they increased with age [2]. These findings are also supported by recent prevalence data from Europe, in which 16,776 interviews were conducted in a population-based survey [3]. The overall prevalence of OAB in those aged ≥40 years was 16.6%, and it increased with age. Frequency was the most commonly reported symptom (85%) while 54% complained of urgency and 36% of urge incontinence.

OAB is a syndrome of storage LUTS defined by the ICS as urgency, with or without urgency urinary incontinence, usually with frequency and nocturia [1]. The symptoms of OAB are presumed to be due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions, when seen during cystometry, are termed DO [1], and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [4]. Antimuscarinic agents remain the first line therapy in the management of patients with OAB. However, antimuscarinics are associated with the typical anticholinergic side-effects of dry mouth, somnolence, constipation and blurred vision, and thus compliance with therapy is often poor. A previous report in women with DO treated with immediate-release (IR) oxybutynin showed only 5.5% were cured of their urinary symptoms and only 18.2% of women continued drug therapy for >6 months [5]. Recently, compliance with tolterodine extended release (ER) and oxybutynin ER was compared with that of oxybutynin IR in a Medicaid population in the USA. Of 1,637 patients starting antimuscarinic medication for OAB, persistence rates at 30 days were only 32% for oxybutynin IR and 44% for oxybutynin ER and tolterodine ER [6]. Consequently there remains a need for a safe and effective treatment for OAB with fewer adverse effects to increase patient compliance and hence persistence [7].

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The lower urinary tract is innervated by both the parasympathetic and the sympathetic nervous systems that act via muscarinic and adrenergic receptors, respectively. During the storage phase continence is maintained by inhibition of the parasympathetic system and by activation of the sympathetic system, which by acting on β_3- and α-adrenergic receptors lead to bladder relaxation and urethral sphincter contraction, respectively. Conversely, during voiding, the pontine micturition centre inhibits the sympathetic system and activates the parasympathetic system, resulting in urethral relaxation and a sustained bladder contraction [8].

ROLE OF α-BLOCKERS IN OVERACTIVE BLADDER

α_1-adrenergic receptors (ARs) mediate the actions of norepinephrine and epinephrine through three α_1-AR subtypes, α_{1A}, α_{1B}, and α_{1D}. In the lower urinary tract, expression of the α_{1A} -AR gene is prominent in the prostate and urethral smooth muscle [9-11]. The α_{1B}-AR subtype is highly expressed in arterial smooth muscle, where stimulation of these receptors triggers contraction and vasoconstriction [12]. The α_{1D}-AR subtype is expressed in the detrusor, prostate, peripheral ganglia, and spinal cord in humans and rats [11-13]. α_1-ARs are also present at parasympathetic nerve terminals in the bladder [14,15]. Recently, Ishihama et al found that the α_{1D}-AR subtype is expressed in the urothelium and affects afferent bladder activity related to adenosine triphosphate [16]. Therefore, it is possible that administration of α_1-AR antagonists will not only improve voiding, but also reduce bladder storage symptoms such as urinary frequency and nocturia.

Terazosin significantly improved storage symptoms in a randomized, controlled trial [17], and prazosin was reported to be effective in suppressing the uninhibited contractions of the detrusor to increase bladder volume [18]. While non-subtype selective α_1-AR blockers relieve voiding and storage symptoms of BPH and BOO, α_{1A}-AR selective blockers relieve only voiding symptoms [19]. Although the exact pharmacological mechanisms remain unclear, recent investigations have suggested that the α_{1D}-AR subtype plays a significant role in regulating detrusor contractility. Tamsulosin has been shown to improve storage as well as voiding conditions in a rat model of BOO [20], although Tatemichi et al [21] found that the selective α_{1A}-blocker silodosin decreased DO in a rat model of BPH. Cold stress induced DO in conscious rats, which was mediated by α_{1A}-AR and α_{1D}-AR subtypes and could be prevented/reduced by α_1-AR antagonists [22]. This suggests silodosin would be suitable for improving irritative symptoms in patients. Thus the α_1-adrenoceptor subtype involved remains to be elucidated. In addition, proposed mechanisms have included actions in the central nervous system and spinal cord. Recently, it has

been postulated that α-blockers may act on sensory neurons of the bladder. α1-blockers are expressed on these neurons in the rat urinary tract and their activation may contribute to the signaling of irritative and nociceptive responses [23]. Yokoyama et al [24] also showed that tamsulosin has an inhibitory effect on C-fiber urethral afferents, thereby improving bladder storage function.

BENIGN PROSTATE HYPERTROPHY WITH OVERACTIVE BLADDER IN MEN

OAB symptoms are as prevalent as BPH, increasing in prevalence among men >40 years old [2]. OAB symptoms are often caused by DO, which may be secondary to BOO [25]. However, DO and OAB symptoms often occur independently of BOO; DO persists in many men after pharmacologic or surgical treatment of BOO [26], and urodynamic studies report that only 48% to 68% of men with LUTS have BOO [27,28]. Several hypotheses have been proposed to explain the etiology of obstructive DO, including post-junctional hypersensitivity, altered adrenoceptor function, afferent nerve dysfunction, imbalance of peptide neuro-transmitters and a primary or acquired myogenic defect [29,30]. Thus, LUTS in men may result from BPH or other conditions leading to OAB.

Pharmacotherapies targeting the prostate such as α1-blockers or 5α-reductase inhibitors (5-ARI) might not completely relieve OAB symptoms [31]. Anti-muscarinic agents are the first-line medical treatment for OAB. However, the use of antimuscarinics is often avoided in men because of the historical concern of an increased risk of urinary retention. Recently, however, several reports have provided evidence that use of tolterodine for 8-12 weeks in men with LUTS is not associated with a decrease in urinary flow or an increase in the rate of acute urinary retention [32-34]. These studies provide evidence that tolterodine at its currently used dose does not decrease detrusor contractility through antimuscatrinic action in the majority of patients. A small percentage of patients who develop difficult urination and acute urinary retention might have a high susceptibility to antimuscarinics or these conditions could be attributed to other unknown causes.

Recently, several studies have shown that combination therapy with anti-muscarinics and α-blockers might improve LUTS in some men more effectively than either agent alone [35-39]. The Tolterodine and Tamsulosin In Men with LUTS including OAB: Evaluation of Efficacy and Safety (TIMES) study [38] found that men meeting symptom criteria for both OAB and BPH who received tolterodine ER plus tamsulosin showed significant improvements in LUTS, based on changes in the total International Prostate Symptom Score (IPSS) and quality-of-life (QoL) item scores, and were more likely to report treatment benefit than men who were in the placebo group. The overall level of improvement for men receiving tolterodine ER plus tamsulosin was greater than that in the groups receiving tolterodine ER or tamsulosin alone. There were no clinically or statistically significant increases in the postvoid residual volume (PVR), maximum flow rate (Qmax), or acute urinary retention requiring catheterization in men receiving tolterodine ER with or without tamsulosin in the TIMES study.

Most previous studies conducted anti-muscarinic add -on therapy to α-blockers in patients with BPH and coexistent OAB, and storage LUTS were confirmed to be improved with the addition of anti-muscarinics [38-41]. Conversely, is it beneficial to add α-blockers to anti-muscarinics in men with LUTS and OAB? The IPSS is an instrument commonly used to assess the severity of LUTS in men [42]. Subscales of the IPSS can discriminate between storage symptoms (IPSS-S) and voiding symptoms (IPSS-E), although the storage subscale does not measure urge incontinence. In recent years, several studies based upon the TIMES study have examined the effects of α-blocker add-on therapy to anti-muscarinics on the storage and voiding subscales of the IPSS [43-46]. Matsuyama et al reported data clarifying if an alpha1-blocker provides additional benefits in combination with anticholinergic treatment in patients with OAB. Although both groups (propiverine alone and combination groups) showed identical improvement of storage symptoms and tolerability, no additional benefits from the α-blocker were observed [43]. However Kaplan et al [44] found tolterodine ER plus tamsulosin therapy, but not tolterodine ER alone, was more effective than a placebo in treating individual storage LUTS assessed by the IPSS in men who met symptom entry criteria for OAB and BPH. Furthermore, Roehrborn et al at [45,46] reported that men with smaller prostates (<29 mL) or lower prostate specific antigen (PSA) levels (<1.3 ng/mL) and moderate-to-severe LUTS including OAB symptoms benefited from tolterodine ER in storage LUTS. Therapy with tolterodine ER plus tamsulosin effectively improved LUTS, including OAB symptoms, in this population, regardless of baseline prostate volume or PSA level. In addition, Rovner et al [47] showed that relative to a placebo, tolterodine ER plus tamsulosin significantly improved daytime and nocturnal urgency episodes, the frequency-urgency sum, subject perception of the level of urgency experienced, and subject perception of the severity of bladder- related problems in men meeting research criteria for OAB and BPH. A significantly greater percentage of subjects treated with tolterodine ER plus tamsulosin reported satisfaction with treatment as well as a willingness to continue treatment. Adding α-blockers to anti-muscarinics seems more beneficial in men with OAB and larger prostates and it might depend on the IPSS subscale.

FEMALE OVERACTIVE BLADDER

OAB symptoms and DO in men are often attributed to obstruction and thus provide a rationale for the use of α-blockers and anti-muscarinics. However, this is seldom the case in women; in a large study of 3,000 women with confirmed DO, only one (0.03%) was found to have bladder neck obstruction in urodynamic evaluation [48]. In addition, α-adrenergic inhibition, resulting in relaxation of the urethral sphincter, has also been shown to lead to stress urinary incontinence in women [49-51]. Therefore, the evidence would suggest that use of α-blockers might unmask stress urinary incontinence or, in women with symptoms of OAB, might lead to urgency becoming urgency incontinence, hence converting OAB 'dry' to OAB 'wet'[52].

Based on the theory that α_{1D}-AR might mediate the overactive symptoms of OAB, several studies have been conducted to discover the efficacy of α-blockers in treating patients with LUTS including OAB [52-54]. Low et al conducted a 14-week, randomized, double-blind, placebo-controlled study to evaluate the effects of terazosin therapy on female LUTS. This study confirmed that terazosin was more effective than a placebo in improving QoL and LUTS in patients with female LUTS, especially those with frequency and straining but no urgency score. In addition, terazosin was safe in patients with LUTS [54]. The finding that urgency was not relieved by terazosin seems to be in line with a report by Robinson and colleagues [52] which showed that

tamsulosin had no effect in women with OAB. Women with OAB were randomized to receive one of four doses of tamsulosin (0.25, 0.5, 1.0 or 1.5 mg), 4 mg of tolterodine ER, or a placebo once daily for 6 weeks. However there were no statistically significant differences for tamsulosin vs a placebo in the mean number of voids/24 h, mean volume voided per void, mean number of incontinence episodes/24 h, mean number of urgency episodes/24 h and QoL. Tamsulosin seems ineffective for treating OAB in women and this would appear to not support its use on an empirical basis. However, whether there might be a synergistic role when used concomitantly with an anti-muscarinic in female OAB remains to be evaluated. Combined therapy might have the advantage of allowing reduced dosing and hence lead to an improvement in tolerability and compliance with therapy.

CONCLUSION

Among men who met symptom-entry criteria for BPH and OAB trials, anti-muscarinics alone could effectively improve OAB and storage symptoms in men with lower baseline prostate volumes. In addition, adding α-blockers to anti-muscarinics seems more beneficial in improving the IPSS-empty and IPSS-storage subscales in men with OAB and larger prostates. α-blockers in general cannot yet be recommended as a treatment for female OAB, but might provide beneficial effects for women with emptying LUTS. The synergistic role when used concomitantly with anti-muscarinics in female OAB remains to be evaluated.

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