Alpha Blockers in the Clinical Treatment of Female Lower Urinary Tract Dysfunction

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ABSTRACT

Female lower urinary tract dysfunction involving symptoms of frequency, urgency, urinary incontinence and voiding dysfunction have been shown to adversely affect quality of life (QoL) and the treatment outcomes have been unsatisfactory. The treatment options include lifestyle modifications, behavioral therapy, pelvic floor muscle training, bladder training and drug therapy. Muscarinic receptor antagonists are the first-line drugs of use. However, they are associated with the typical anticholinergic side-effects of dry mouth, somnolence, constipation and blurred vision, and thus compliance with therapy is often poor. α-adrenergic receptor antagonists are currently used in men with lower urinary tract symptoms. A selective α_1-adrenoceptor antagonist that is known to have greater specificity for α_1-A and α_1-D receptors than for α_1-B receptors might have a role in the management of overactive bladder in women. A selective α_1-adrenoceptor antagonist such as terazosin is effective in improving the quality of life and female lower urinary tract symptoms, especially in those with frequency and straining. Yet, it is ineffective for treating overactive bladder in women.

Keywords: alpha-blocker, female, lower urinary tract dysfunctions, treatment

INTRODUCTION

Epidemiological studies have reported the overall prevalence of female lower urinary tract symptoms (FLUTS) to be as high as 19% [1, 2]. In one study, frequency was the most commonly reported symptom (85%) in those with overactive bladder (OAB) symptoms, while 54% complained of urgency and 36% of urge incontinence [3]. FLUTS have been shown to adversely affect quality of life (QoL), but unfortunately, treatment outcomes for FLUTS have been unsatisfactory [4].

DEFINITION OF FEMALE LOWER URINARY TRACT SYMPTOMS

The lower urinary tract consists of the urinary bladder and urethra. Two principal functions of the urinary bladder are urine storage and emptying. The urethra maintains urinary continence by relaxing during the voiding phase and contracting during the urine storage phase [5].

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According to the new International Continence Society (ICS) definition [6], lower urinary tract symptoms (LUTS) can be divided into the following three groups: (1) storage symptoms, which include increased daytime frequency, nocturia, urgency and urinary incontinence; (2) voiding symptoms, which include slow stream, splitting or spraying, intermittent stream, hesitancy, straining and terminal dribble; and (3) post micturition symptoms, which include a feeling of incomplete emptying and post micturition dribble. Male and female LUTS have similar characteristics even if they can have extremely different causes.

PATHOPHYSIOLOGY LINKING THE TREATMENT OPTIONS

The lower urinary tract is innervated by both the parasympathetic and sympathetic nervous system, that act via muscarinic and adrenergic receptors, respectively [7]. During the storage phase, continence is maintained by inhibition of the parasympathetic system and activation of the sympathetic β_3 adrenergic receptors which cause relaxation of the detrusor muscle. Conversely during voiding, the pontine micturition center inhibits the sympathetic system and activates the parasympathetic system by acting on acetylcholine-induced stimulation of bladder muscarinic receptors, resulting in urethral relaxation and a sustained bladder contraction.

OAB is currently the most common term used in clinical medicine to describe a complex of LUTS [6]. The core symptom of OAB is urgency and it also consists of frequency, nocturia, and, occasionally, urge urinary incontinence. 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 detrusor overactivity (DO) [6], and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [8]. Behavioural modification and drug therapy with muscarinic receptor antagonists remain integral in the management of women with OAB [9,10].

First-line treatments for OAB include lifestyle modification, behavioral therapy, pelvic floor muscle training, and bladder training. Muscarinic receptor antagonists are the first-line drug therapy [9,10]. However, they are associated with the typical anticholinergic side-effects of dry mouth, somnolence, constipation and blurred vision, and thus compliance with therapy is often poor [9,10].

α_1-adrenergic receptors are found at the bladder neck and three subtypes have been identified, α_1-A, α_1-B and α_1-D [11]. Those receptors present in the bladder are predominantly α_1-A and α_1-D, while α_1-B receptors are found in the vasculature and are involved in blood pressure control. Consequently α_1-adrenergic blocking agents with subselectivity for α_1-A and α_1-D might be most useful in the manage-

ment of lower urinary tract dysfunction. It has been speculated that the α_1-D receptor might mediate the overactive symptoms of OAB, while the α_1-A receptor subtype mediates the obstructive symptoms [12].

Currently, α-adrenergic receptor antagonists are used for men with LUTS [13]. Treatment with these agents is often initiated on the assumption that these urinary tract symptoms are caused by benign prostatic hyperplasia (BPH). The treatment benefits with α-adrenergic receptor antagonists occur mainly through reducing smooth muscle tone in the prostate and bladder neck and decreasing bladder outlet resistance. In those cases where LUTS are thought to be secondary to bladder outlet obstruction caused by BPH, tamsulosin has been shown to produce a significant decrease in detrusor pressure, increase in flow rate and concomitant improvement in symptoms [13]. Tamsulosin is a potent, specific and selective α_1-adrenoceptor antagonist that is known to have greater specificity for α_1-A and α_1-D receptors than for α_1-B [14], and thus might have a role in the management of OAB in women.

CLINICAL EVIDENCE OF α-ADRENERGIC RECEPTOR ANTAGONIST EFFECTS IN FEMALE LOWER URINARY TRACT SYMPTOMS

There is currently little objective evidence to support the efficacy of tamsulosin in OAB. Anecdotal evidence shows that it might improve urinary symptoms secondary to DO in men [15], and for some time it has been used 'off label' in women with symptoms suggestive of OAB [16]. In addition α_1-adrenergic receptors have been shown to be increased in patients with DO [11]. In a randomized double-blind placebo-controlled multicenter study which explored the efficacy and safety of tamsulosin and tolterodine, 364 women with symptoms of OAB for ≥3 months 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 [17]. The mean number of void/24 h, mean volume voided per void, mean number of incontinence episodes/24 h, mean number of urgency episodes/24 h and quality of life (QoL) were not significantly different between the tamsulosin and placebo groups. In contrast, women taking tolterodine ER 4 mg had a consistently greater increase in the mean voided volume/void and consistent decreases in incontinence episodes/24 h, urgency episodes/24 h and episodes of nocturia/24 h, but it was not statistically significant. They concluded that tamsulosin is not effective for treating OAB in women and suggested it should not be used on an empirical basis. However, they did show that compliance with tamsulosin therapy was good with a low (4.7%) proportion of women discontinuing use because of adverse events [17]. These results are supported by International Consultation on Incontinence (ICI) recommendations on drugs for OAB [18]. Recommendations on α-adrenoceptor antagonists for OAB treatment were graded C (optional).

α-adrenoceptor antagonists might have a role in the management of frequency as a predominant LUTS in women. Serels et al showed that the expanded American Urological Association (AUA) scores of 34 women with symptoms of frequency and urgency were reduced after doxazosin (2 mg once daily) was given as monotherapy for 1 or more months [19]. A large randomized, double-blind, placebo controlled trial of terazosin therapy for patients with FLUTS was conducted by Low et al [20]. A total of of 100 females 20 to 70 years old who met the inclusion criteria of International Prostate Symptom Score (I-PSS) ≥8 and symptom duration 1 or more months were enrolled. Subjects were randomized to receive terazosin or a placebo in titrated doses (1 mg once daily, 1 mg twice daily to 2 mg twice daily) for 14 weeks. Using the I-PSS scoring system, 32 of 40 (80%) subjects who received terazosin responded in contrast to 22 of 40 (55%) of those taking a placebo ($p<0.02$). Of the 7 I-PSS individual item scores, only the item scores for frequency and straining showed statistically significant reductions with terazosin ($p<0.01$). All King's Health Questionnaire quality of life domains except the domain of severity measures showed statistically significant improvements with terazosin therapy ($p<0.05$). Twenty three of 40 evaluable subjects (58%) on a placebo experienced adverse events vs 16 of 40 (40%) on terazosin ($p>0.05$). They concluded that terazosin is safe, as well as more effective than a placebo in patients with FLUTS.

The present evidence suggests that an α_1-adrenoceptor antagonist (tamsulosin) alone is not clinically useful in the management of women with symptoms of OAB. However, an α_1-adrenoceptor antagonist (terazosin) is effective in patients with urinary symptoms of frequency, as shown by analysis of I-PSS individual item scores. Terazosin was chosen for the FLUTS treatment study based on the proposed hypothesis that a nonsubtype selective α_1- adrenergic receptor antagonist or an α_1-A/D- adrenergic receptor selective antagonist can antagonize the activity of bladder α_1-A, α_1-D adrenergic receptors and urethra α_1-A adrenergic receptors. It was postulated that bladder α_1-D adrenergic receptors and urethra α_1-A adrenergic receptors may cause storage and voiding symptoms, respectively [12, 16].

A possible explanation of mechanisms responsible for the improvement in frequency and QoL scores with terazosin is that this drug might act on the urethra α_1A adrenergic receptors, thus reducing bladder outlet obstruction. Hence, frequency of urination is reduced. On the other hand, 2 mg. Of terazosin twice daily might not be sufficient to demonstrate antagonistic activity of α_1A adrenergic receptor antagonists on α_1D adrenergic receptors (bladder and/or extraprostatic sites of action).

OAB symptoms and DO signs are attributed to obstruction in men. This provided a rationale for the use of α_1- adrenergic receptor antagonists 'off label' in women with OAB symptoms. Yet, DO associated with bladder neck obstruction occurs in only 0.03% of women with OAB. [21]. In addition, while the incidence of DO is known to increase after continence surgery, this represents only a minority of cases [22]. Pharmacotherapies that target only the prostate (and not the bladder) may not alleviate OAB symptoms in women, as these symptoms are not caused by a prostate condition [23]. Furthermore, a dose of 1.5 mg tamsulosin daily might not be sufficient to demonstrate antagonistic activity of α_1 adrenergic receptor antagonists on α_1D adrenergic receptors(bladder and/or extraprostatic sites of action).

Adverse events observed from α_1 adrenergic receptor antagonists are mild. These findings often involve decreases in blood pressure and the speed of onset of these decreases [24]. Furthermore, α-adrenergic inhibition, resulting in relaxation of the urethral sphincter, has been shown to lead to stress urinary incontinence in women [25], and was documented to result in changes in maximum urethral closure pressure [25]. In a large retrospective study of Australian women, the incidence of urodynamic stress incontinence was significantly higher in those taking prazosin than in those not taking this drug (86.2% vs 65.7%; $P<0.01$). The urinary incontinence of 25 of 45 women contacted

was improved or cured with prazosin withdrawal [26]. Consequently, the evidence would suggest that use of α_1-adrenergic receptor antagonists 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'.

CONCLUSION

In conclusion, a selective α_1-adrenoceptor antagonist, terazosin, is effective in improving QoL and LUTS of patients with FLUTS especially those with urinary symptoms of frequency and straining to void. Terazosin is safe in patients with FLUTS. On other hand, the selective α_1-adrenoceptor antagonist tamsulosin is ineffective for treating OAB in women. The evidence appears not to support its use on an empirical basis. Whether there might be a synergistic role when used concomitantly with an antimuscarinic agent remains to be evaluated. Combined therapy might have the advantage of allowing reduced doses and hence lead to improvements in tolerability and compliance with therapy.

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