Current pharmacotherapy of lower urinary tract symptoms

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Abstract

Lower urinary symptoms (LUTS), including the overactive bladder (OAB) syndrome, can be found in 10—15% of all men and women and often have major effects on quality of life and social functioning. The first line of pharmacological treatment of OAB in women has been and still is antimuscarinic drugs. In men α_1-adrenoceptor (AR) antagonists remain the standard treatment of LUTS. However, recent advances in the physiology/pathophysiology of LUTS/OAB, recognizing the functional contribution of the urothelium, the spontaneous myocyte activity during bladder filling, and the diversity of nerve transmitters involved, have sparked interest in novel possibilities to treat these conditions. For example, new, selective α_1-AR antagonists (naftopidil, silodosin), β_3-AR agonists (mirabegron), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil), combinations (α_1-AR antagonist + antimuscarinic), and drugs with a central mode of action (duloxetine, tramadol) all have positive proof of concept documented in randomized, controlled trials. Which of these therapeutic principles will be developed as clinically useful treatments remains to be established.

Keywords α_1-Adrecoceptor antagonists; β_3-adrenoceptor agonists; incontinence; phosphodiesterase inhibitors; urgency

Introduction

According to the International Continence Society (ICS), lower urinary tract symptoms (LUTS) can be divided into three groups: storage symptoms, voiding symptoms, and post-micturition symptoms. LUTS in men typically occur in association with bladder outlet obstruction (BOO) secondary to benign prostatic hyperplasia (BPH); however, the two conditions do not invariably coexist. Thus, male LUTS might be due neither to BOO nor prostatic disease. In women, LUTS have usually been equal to the overactive bladder (OAB) syndrome, and assumed to be caused by detrusor overactivity (DO), even if this does not always seem to be the case. Irwin et al.,[1] studying 19,000 adult men and women, confirmed that OAB is not solely a female disorder. They found that the prevalence in both sexes was around 12% and that it increases with age. They also found that in men, the prevalence of storage LUTS (suggestive of OAB) was twice as common as voiding LUTS. Concerning pathophysiology of storage symptoms in men, focus has shifted from the prostate to the bladder as the source of some LUTS, and as a therapeutic target. This has created a renewed interest in OAB drugs for treatment of male LUTS, and also opened the door for combinations of drugs.

Available information thus suggests that LUTS are a non-sex-specific, non-organ specific group of symptoms, which are sometimes age-related and progressive, and a broader clinical perspective has been advocated: all LUTS should be treated, not just selected symptoms. Since the pathophysiology of LUTS/OAB is multifactorial, there are many potential targets for future drugs, as identified in preclinical investigations.[2] However, it is difficult to predict what principles can be applied clinically. The present overview focuses on principles for which positive proof of concept are available.

Peripherally acting drugs

Subtype selective α_1-adrenoceptor antagonists

Currently used α_1-adrenoceptor (AR) antagonists are effective for treatment of both storage and voiding LUTS associated with, or suggestive of, BPH. However, in females with OAB α_1-AR antagonists seem to be ineffective. In a randomized controlled trial (RCT), comprising 364 women with OAB, no effect of tamsulosin vs placebo could be demonstrated.[3] On the other hand, voiding symptoms in women with functional outflow obstruction, or LUTS, were successfully treated with an α_1-AR antagonist. The main question is whether better efficacy and/or tolerability can be obtained by highly subtype selective drugs than with the commonly used alternatives. Selectivity for α_{1B}-AR has been considered disadvantageous from a cardiovascular point of view. Is selectivity for α_{1A}-, α_{1D}-, or $\alpha_{1A/D}$-ARs the most favourable?

In males, it has been assumed that the targets for α_1-AR antagonists were to be found in the *prostate* and other parts of the LUT. Kojima et al.[4] studied the expression of α_1-AR in the transitional zone of prostates from 55 patients with BPH, comparing patients treated with tamsulosin presumed to block α_{1A}-ARs and naftopidil presumed to block α_{1D}-ARs. However, the selectivity of naftopidil for α_{1D}- vs α_{1A}-ARs is modest and its use as a tool to separate between α_1-AR subtypes is questionable. Nevertheless, the tamsulosin and naftopidil groups were classified as α_{1A}-AR dominant (22 and 12 patients) and α_{1D}-AR dominant (11 and 16 patients, respectively). The efficacy of tamsulosin and naftopidil differed depending on the dominant expression of the α_1-AR subtype in the prostate. Tamsulosin was more effective in patients with dominant expression of the α_{1A}-AR subtype, whereas naftopidil was more effective in those with dominant expression of the α_{1D}-AR subtype. In another study, the same group assessed whether there was a direct correlation between the prostatic expression of α_1-AR subtype mRNA and severity of LUTS or bladder outlet obstruction,[5] but no such correlation was found. Kojima et al.[5] concluded that the expression level of α_1-AR subtype mRNA in the prostate could be a predictor of the efficacy of subtype selective α_1-AR antagonists in patients with BPH, and suggested that genetic differences were responsible for the diverse responses to the drugs.

Silodosin (KD-3213), which has a high selectivity for α_{1A}-ARs, had clinically good effects on both voiding and storage

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symptoms.[6,7] Chapple et al.[7] conducted a multicentre, double-blind, placebo- and active-controlled parallel group study comparing silodosin, tamsulosin, and placebo. A total of 1228 men aged 50 years or older with an International Prostate Symptom Score (IPSS) $\geq$13 and a urine maximum flow rate (Q_{max}) >4 and $\leq$15 ml/second were selected at 72 sites in 11 European countries. The patients were entered into a 2-week wash-out and a 4-week placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg ($n = 381$), tamsulosin 0.4 mg ($n = 384$), or placebo ($n = 190$) once daily for 12 weeks. Its overall efficacy was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo. There was no significant difference between the two α_1-AR antagonists and the placebo in terms of Q_{max}. There was also no difference between the two α_1-AR antagonists for the QoL parameter, whereas both were better than the placebo. Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1%, 1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively). The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α_{1A}-AR antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment due to this adverse event.

It thus seems that selective blockade of α_{1A}-ARs is a clinically effective approach, and silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in patients with LUTS, even if treatment is associated with a high incidence of ejaculatory dysfunction.

Interest has also been focussed on the α_{1D}-ARs, which predominate in the human *bladder*, assuming that these receptors are responsible for storage symptoms. However, the relationship between the α_{1D}-ARs in the human detrusor smooth muscle and the pathophysiology of LUTS is unclear. Ikemoto et al.[8] gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the IPSS for storage symptoms, tamsulosin monotherapy decreased the IPSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α_1-AR subtypes between the drugs) could not be reproduced in a randomized head-to-head comparison between the drugs.[9] Based on available evidence, it therefore cannot be concluded that the α_{1D}-ARs on the detrusor smooth muscle are the main therapeutic target. However, α_{1D}-ARs may have effects on different locations in the bladder beside the detrusor smooth muscle: the detrusor vasculature, the urothelium, and the afferent and efferent nerve terminals and intramural ganglia. The importance of this remains to be established.

It seems that beside using the non-subtype selective α_1-AR antagonists, selective targeting of either α_{1A}- (silodosin) or $\alpha_{1A/D}$-ARs (tamsulosin, naftopidil) are clinically effective approaches. In the absence of clinically available drugs with a high selectivity for α_{1D}-ARs, the importance of this receptor subtype remains unclear. Considering the high frequency of ejaculatory dysfunction with silodosin, drugs with a higher (compared to presently available drugs), but balanced selectivity for $\alpha_{1A/D}$-AR over α_{1B}-ARs, may be the best option for treatment of male LUTS/OAB.

Antimuscarinic agents

Current guidelines recommend the use of oral antimuscarinics (anticholinergics) as first-line pharmacologic therapy for the management of OAB/DO. The drugs are recognized as safe and effective in the treatment of these conditions.[10–12]

Acetylcholine (ACh) is released not only from parasympathetic efferent nerves in the bladder, but can also be produced and released from non-neuronal sources, including the urothelium. Antimuscarinic agents competitively inhibit the effects of ACh at post-junctional muscarinic receptors on bladder wall structures, as well as on tissues and organs outside the bladder. The detrusor muscle contains mainly type 2 and 3 muscarinic receptors (M_2 and M_3), with M_3 receptors considered to be the most important for detrusor contraction. The function of M_2 receptors has yet to be clearly defined, but it has been suggested that these might have an indirect role in mediating bladder contractions by enhancing M_3-receptor mediated effects. Muscarinic receptors have been detected on the urothelium, on suburothelial interstitial cells and afferent nerves. The urothelium/suburothelium is now believed to play a role in bladder sensory mechanisms via activation of local afferent nerves which monitor the volume of the bladder and the amplitude of bladder contraction.

The traditional view has been that the antimuscarinics inhibit voluntary and involuntary bladder contractions by blocking the muscarinic receptors on the detrusor muscle cells. This is probably not the only way in which they act. The main effects in OAB are exerted during the filling phase during which antimuscarinics may reduce detrusor activity and improve bladder capacity via direct inhibition of bladder afferent signalling at the level of the urothelium and suburothelium.[13]

Seven antimuscarinic agents are currently recommended for the treatment of OAB/DO: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.[12] Large, randomized, placebo-controlled studies have demonstrated that patients receiving these agents report significant reductions in urinary frequency, urgency episodes and urgency urinary incontinence.[11] A meta-analysis of clinical trials involving over 10,000 patients evaluated antimuscarinic agents together as a whole versus placebo in adult patients with OAB or a urodynamic diagnosis of DO, or both.[11] Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence episodes per day and from 0.5 to 1.3 micturitions per day. In addition, significant improvements in health-related quality of life measures have been demonstrated.[14]

Little difference in efficacy exists between antimuscarinic agents as seen in comparative studies, but clinically significant differences in adverse effects cannot be excluded.[10–12] Such differences may be related to differences in the route of administration (oral versus transdermal), relative affinities for human muscarinic receptor subtypes, or to whether the formulation is immediate release (IR) or extended release (ER).

Therapy for detrusor overactivity is usually long term, and the incidence of antimuscarinic-induced adverse events is relatively high. The common adverse events are the expected side effects of antimuscarinic drugs and result from the blockade of muscarinic