Antimuscarinics, β-3 Agonists, and Phosphodiesterase Inhibitors in the Treatment of Male Lower Urinary Tract Symptoms

An Evolving Paradigm

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KEYWORDS

• Lower urinary tract symptoms • Storage LUTS • Phosphodiesterase inhibitors • Antimuscarinics • β-3 Agonists

KEY POINTS

- Storage lower urinary tract symptoms (LUTS; including overactive bladder [OAB]) are most bothersome for patients and are likely to have an etiopathogenesis related to bladder function and abnormality affecting the bladder outlet.
- Several pharmacotherapies (antimuscarinics, β-3 agonist, and phosphodiesterase inhibitors) have emerged over the past decade, which show good efficacy and safety in the treatment of men with storage LUTS/OAB.
- The optimal place of these agents in the treatment algorithm will need to be decided by further studies assessing comparative efficacy and responder characteristics, with attention to the potential for combination therapy.

INTRODUCTION

Lower urinary tract symptoms (LUTS) occur frequently in older men[1] and are often bothersome with a negative impact on quality of life (QOL).[2] In most individuals, voiding and storage LUTS will coexist,[3] but storage LUTS are typically more bothersome.[4] Before the past decade, most therapeutic interventions were targeted at relieving voiding LUTS, through an effect on the prostate gland with the assumption that benign prostatic hyperplasia (BPH) was the main etiologic factor. In recent times, the influence of the bladder and in particular the afferent system on the development of storage LUTS has become widely accepted, which has changed the paradigm for the management of male LUTS away from a traditional view of treating BPH, and the development

Conflicts of Interest: N.I. Osman has received speaker fees and an educational grant from Astellas. R. Aldamanhori has no conflicts of interest to disclose. A. Mangera has received speaker fees and an educational grant from Astellas. C.R. Chapple is a researcher and speaker for Astellas, Pfizer, Recordati, Lilly and Allergan.

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Urol Clin N Am 43 (2016) 337–349
http://dx.doi.org/10.1016/j.ucl.2016.04.004

of new pharmacotherapeutic approaches has emerged.[5]

Overactive bladder (OAB) is a symptom complex that consists of an important and highly bothersome subset of storage LUTS and is defined as "urinary urgency with or without urgency incontinence usually accompanied by frequency and nocturia."[6] The sine qua non of OAB is urinary urgency, defined as "the sudden and compelling desire to void that is difficult to defer."[6] In men, OAB is often associated with detrusor overactivity, occurring in 69% and 90% of individuals with OAB without incontinence (OAB-dry) and OAB with incontinence (OAB-wet), respectively.[7]

Although for many years antimuscarinic agents were avoided in men due to the concern about causing urinary retention, there is now a strong evidence base to support the safety and efficacy of this class in treating male patients with storage LUTS/OAB. More recently, 2 new agents have been introduced into the therapeutic armamentarium in the treatment of male LUTS: the β-3 agonist and phosphodiesterase inhibitors. This article discusses the mechanism of action of these 3 agents in the context of the pathophysiology of LUTS/BPH in men before focusing on the evidence relating to their efficacy and safety.

ANTIMUSCARINICS

Mechanism of Action

Antimuscarinic agents act to some extent on the afferent (based on preclinical data) innervations, but probably principally on the parasympathetic (efferent) system. The chief functional receptor responsible for the motor activity of the detrusor muscle is the postjunctional muscarinic M_3 receptor.[8] Although the most numerous (75%) are the M_2 receptors, their function in the bladder along with that of M_4 and M_5 remains undefined.[9] The M_1 muscarinic receptors predominate in the central nervous system; M_1 and M_3 in salivary glands, M_2 and M_3 in the gastrointestinal tract, M_3 and M_5 in the eyes, and M_2 in the heart.[10]

M_3 receptor excitation leads to smooth muscle contraction via entry of extracellular calcium into the cell through L-type channels and activation of rho kinase.[11] Although there has been discussion about the potential importance of activity on M_2 receptors and sensory nerves and there is a body of literature to support this, these putative mechanisms of action still remain the subject of academic discussion.

In addition, neurotransmitters are released from the urothelium and suburothelium in response to distension and receptor activation.[12] Acetylcholine (Ach) has been shown to be released in greater amounts when the urothelium of bladder strips is intact, suggesting nonneuronal crosstalk between the urothelium and detrusor muscle.[13] It is also proposed that this nonneuronal Ach may enhance muscarinic receptor-mediated detrusor activity and may also be inhibited by antimuscarinic agents to different degrees.[14] Therefore, inhibition of smooth muscle "micromotion" may occur, a phenomenon that is postulated to occur because of leak of Ach from postganglionic parasympathetic nerve during the storage phase of micturition leading to activation of sensory afferent fibers and the sensation of urgency.[15] Recent work has also suggested that muscarinic activation also stimulates urothelial adenosine triphosphate release,[16] which may be of importance given that changes in purinergic signaling have been implicated in the aging bladder and are postulated to occur in bladder dysfunction.[17]

Current antimuscarinic agents approved by the regulatory authorities include oxybutynin, tolterodine, solifenacin, darifenacin, trospium, propiverine, and fesoterodine. The above antimuscarinic agents have different affinities for the different muscarinic receptors,[18] and darifenacin is the only agent with a high selectivity for the M_3 receptor over M_2.[19] Fesoterodine is an oral antimuscarinic drug that is metabolized rapidly and extensively to 5-hydroxymethyl tolterodine, the main active metabolite of tolterodine.[20] Tolterodine and its 5-hydroxymethyl metabolite (fesoterodine) do not discriminate between the receptor subtypes. Oxybutynin and solifenacin show fractional selectivity for M_3 receptors.

In animal models, greater bladder selectivity has been shown for tolterodine,[21] darifenacin,[22] and solifenacin[23] compared with oxybutynin. It should be noted that animal studies cannot be translated directly to the human situation, and this data should be interpreted with that in mind. Trospium chloride is a quaternary amine that is incompletely absorbed or metabolized, and the majority is excreted in the urine and therefore has a high bioavailability.[24] In addition to antimuscarinic activity, propiverine has been shown to antagonize Ca^{2+} channels, which may suppress smooth muscle contraction resistant to atropine.[25]

Clinical Efficacy

Two meta-analyses have reviewed anticholinergic medication use in patients with LUTS.[26,27] Some of the drugs are available as immediate release or once daily preparations, such as oxybutynin, propiverine, tolterodine, and trospium. In addition, oxybutynin is available as a transdermal patch and as a topical gel. Most of the trials in the