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Collaborative Review – Bladder Outlet Obstruction

The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

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Abstract

Context: This review focuses on the contemporary role of antimuscarinics in the management of men with symptoms of bladder outlet obstruction (BOO) and concomitant overactive bladder (OAB). Safety issues of antimuscarinics in this subpopulation of men are also reviewed.
Objective: We reviewed the current literature and performed an analysis of the efficacy, suitability, and the safety of antimuscarinics in this subpopulation of men.
Evidence acquisition: We performed a systematic search of Medline/PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews for relevant articles published between 1990 and September 2010, restricted to studies in humans published in English. In addition, published abstracts presented at the annual meetings of the European Association of Urology, the American Urological Association, and the International Continence Society in the last decade (2000–2010) were hand-searched and evaluated. Each article's title and abstract were reviewed for their appropriateness and relevance to the use of antimuscarinics in patients with BOO and concomitant OAB. Relevant articles were fully reviewed and included in the final data acquisition.
Evidence synthesis: Treatment options include combination treatment with α- blockers and antimuscarinics, sequential use of α-blockers and antimuscarinics, monotherapy with antimuscarinics, and a combination of antimuscarinics and 5α-reductase inhibitors. The sequential use of α-blockers and antimuscarinics seems to be the most appropriate approach, and the use of antimuscarinics and α-blockers appears generally to be safe and efficacious. Data are insufficient for a possible stratification of patients for a specific sequence of the drugs reviewed.
Conclusions: This review infers that the existing data confirm the safety of antimuscarinics administered for the treatment of these patients. The efficacy of antimuscarinics has been proven in different trials regarding different storage symptom end points, but not all end points regarding OAB reached significance. All the reported trials are of short duration (4–12 wk) and include only men with low postvoid residual urine volumes at baseline (<200 ml). Overall, the addition of an antimuscarinic to the treatment of a patient with BOO and concomitant OAB seems to offer an amelioration of the symptoms and a moderate improvement in quality of life.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a common condition among elderly men, occurring in up to 70% of men >60 yr of age [1], and is commonly the cause of bladder outlet obstruction (BOO). Although the immediate impact of BOO is on voiding and postvoiding symptoms, lower urinary tract symptoms (LUTS) associated with the disorder include storage symptoms [2]. These symptoms are particularly bothersome to patients, interfere with daily activities, and have a negative impact on patient quality of life (QoL) [3].

Overactive bladder (OAB) is a symptom complex defined by urgency with or without urge urinary incontinence usually associated with increased daytime frequency and nocturia [4]. The most common cause of OAB is detrusor overactivity (DO) in half to two-thirds of patients [5], which is thought to result not only from efferent (motor) hyperfunction/dysfunction but also most likely by afferent (sensory) noise [6–9]. Afferent noise may be generated by local acetylcholine (ACh) release within the detrusor muscle. Moreover, ACh derived from urothelium may stimulate afferent activity (probably via release of adenosine triphosphate) from the bladder, contributing to OAB and DO [8]. It has been suggested that those patients with OAB but without urodynamically demonstrable DO could represent a different part of the same disease spectrum [10]. Interestingly, patients with OAB seem to respond to antimuscarinic treatment irrespective of the presence of DO [11].

DO has been identified in approximately 45–50% of men with BOO and could result from local factors within the bladder, such as denervation hypersensitivity of cholinergic receptors (Cannon's law) and/or structural changes resulting from urinary bladder ischaemia [12]. Not only peripheral problems (BOO and bladder) but even central problems, such as ischaemic brain lesions, can provoke OAB, especially in the elderly population [7]. However, the presence of BOO and DO does not necessarily imply a cause–effect relationship, because OAB symptoms can occur in patients without BOO [12] (Fig. 1), suggesting that it is an age-related phenomenon. Pressure-flow testing is the only way to confirm the presence of BOO in men presenting with one or more LUTS.

Alfa1-adrenoceptor antagonists (α-blockers) remain the most widely used pharmacologic agents for relief of bladder outflow resistance and are targeted at the dynamic component (increased smooth muscle tone) of BPH [13]. Considering the prevalence and severity of storage symptoms in male patients with increasing age, it could be reasonably expected that a combination therapy comprising an α-blocker and an antimuscarinic agent would significantly alleviate storage LUTS after primary treatment with the α-blocker and further improve patient QoL. However, there is the theoretical danger of impairment of already-decompensating bladder activity in the presence of obstruction as a consequence of antimuscarinic action, thereby precipitating acute urinary retention (AUR). For many years, the diagnosis of BPH and BOO has been considered a contraindication to the use of antimuscarinics.

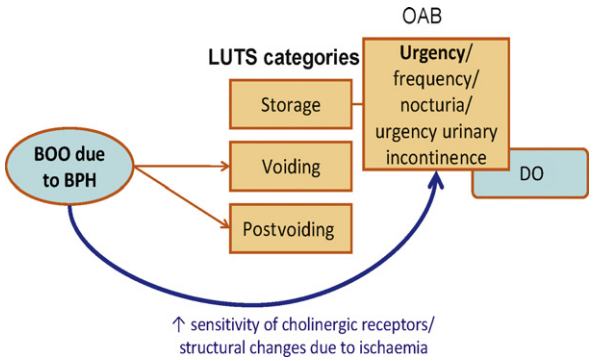

Fig. 1 – Lower urinary tract symptoms (LUTS) involved in benign prostatic hyperplasia (BPH)–associated bladder outlet obstruction (BOO) and overactive bladder (OAB). BOO resulting from BPH can lead directly to voiding and postvoiding LUTS. OAB symptoms are often associated with detrusor overactivity (DO) identifiable on urodynamic testing.

Although traditionally, antimuscarinic therapy at therapeutic doses has been assumed to work via motor pathways, there is an increasing body of evidence that the mechanism of action of antimuscarinics on OAB symptoms could be on bladder sensory pathways rather than on motor pathways [8,14,15]. Accordingly, antimuscarinics administered at clinically recommended doses have little effect on voiding pressures [8,16].

There is some evidence that muscarinic acetylcholine receptors located in the urothelium/suburothelium and on afferent nerves may contribute to the pathophysiology of OAB. Blockade of these receptors may also contribute to the clinical efficacy of antimuscarinic agents [8,17]. Muscarinic receptors are also known to be expressed on sympathetic nerve endings, where they play a regulatory role in the release of norepinephrine [18,19]. Moreover, it has been proposed that there is an activation of C-fibres in pathologic situations without having a significant role in the physiologic sensation of bladder filling. The non-neuronal release of neurotransmitters may also represent another mechanism of a direct stimulatory effect on C-fibres [20,21]. In support of this hypothesis, Hedlund et al [22] showed in an animal study that tolterodine did not decrease the contractile effects of apomorphine-induced detrusor contractions at the doses used, suggesting that the drug had no effect on efferent neurotransmission during voiding. It is of interest also that in a recent study, Fullhase et al [23] concluded that urodynamic changes in obstructed rats can be normalised by intrathecal 5-hydroxymethyl tolterodine and by intrathecal doxazosin. When the two drugs were combined at the doses used, only small additional effects were observed. The central pathways on which the two drugs act seem to be upregulated in rats with partial urethral obstruction, but the effect appears to be less relevant under physiologic conditions (nonobstruction).

A further important consideration is the direct action of antimuscarinics on possible antimuscarinic receptors of the prostate. Witte et al [24] reported the existence of dense cholinergic innervations in the prostate within both the stromal and epithelial compartments of the prostatic gland. Interestingly, the muscarinic receptors of the human