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Do Antimuscarinics Affect Voiding Function during the Treatment of Overactive Bladder

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ABSTRACT

The safety and efficacy of antimuscarinics in the treatment of overactive bladder syndrome (OAB) are not well established. A literature survey of basic and clinical publications relevant to the use of antimuscarinics in OAB was carried out using the PubMed database. The results in terms of safety and efficacy from evidence-based clinical trails were specifically emphasized. During the storage phase, acetylcholine may be released from both neuronal and non-neuronal source and directly or indirectly excite afferent nerves in suburothelium and within the detrusor. This mechanism is important in the pathophysiology of OAB and the major target for the antimuscarinic drugs. Under the concept of sensory inhibition, the application of the antimuscarinics is most extensive in the treatment of overactive bladder induced by bladder outlet obstruction and neurogenic detrusor overactivity. The available data may be considered promising and the use of antimuscarinics has been demonstrated to be a quite safe approach to the treatment of OAB. Improvement in the patient's quality of life and lower urinary tract symptoms are indicative of the clinical value of the use of antimuscarinics for the treatment of OAB. *Key words:* bladder, overactive bladder, antimuscarinics, detrusor overactivity.

Overactive bladder (OAB) is a symptom complex defined by the International Continence Society [1] and includes urinary urgency, urgent incontinence, frequency and nocturia. The major causes of OAB are a sensory disturbance of the bladder, a low functional bladder capacity and polyuria [2]. The presence of low functional bladder capacity can be evaluated by urodynamic studies. Either detrusor underactivity or detrusor overactivity could lead to a low functional capacity and induced OAB in humans [2]. The first-line pharmacological treatment of OAB has been and still is antimuscarinics. There is much evidence that this treatment is not always effective and that it can be associated with side effects [3]. The rationale for the use of antimuscarinics drugs in the management of OAB needs to be fully established.

CURRENT CONCEPTS OF HOW ANTIMUSCARINICS ACTS ON THE BLADDER

OAB caused by detrusor overactivity and sensory disturbance of the bladder are indications for the use of antimuscarinics. The major subtypes of muscarinic receptors that affect voiding function are the M_2 and M_3 receptors [2,3]. The roles of the autonomic signal transduction pathway involving M_2 and M_3 receptors in the bladder are shown in the Fig. 1. The M_3 receptors are mainly responsible for normal micturition contraction. Acetylcholine interacts with the M_3 muscarinic receptors and activates phospholipase C through coupling with G protein. This generates inositol triphosphate, which causes the contraction of the detrusor muscle. The M_2 receptors may contribute to bladder contraction by inhibiting adenylate cyclase activity and decreasing intracellular cyclic adenosine monophosphate levels, which mediate bladder relaxation. The common view is that in cases with detrusor overactivity, the antimuscarinics block the muscarinic receptors on the detrusor muscle and decreases the ability of the bladder to contract. However, there is little evidence for a significant reduction of voiding contraction during the treatment of the patients with OAB [3]. In fact, most antimuscarinic drugs are competitive antagonists. This characteristic implies that when there is a massive release of acetylcholine during the voiding phase, the effectiveness of these drugs is decreased; otherwise, the reduced ability of the detrusor to contract would led to urinary retention. Currently, the effect of antimuscarinics on the urothelium level is being more emphasized [4]. The urothelium functions not only as a barrier against urea and ion diffusion, but also as a sensor that helps to control bladder function and dysfunction. During the storage phase, acetylcholine may be released from both neuronal and non-neuronal source and directly or indirectly excite afferent nerves in suburothelium and within the detrusor (Fig. 2). This mechanism is important to the pathophysiology of OAB and is likely to be the major target for antimuscarinic drugs [3].

THE APPLICATIONS OF ANTIMUSCARINICS IN PATIENTS WITH BLADDER OUTLET OBSTRUCTION OR NEUROGENIC DETRUSOR OVERACTIVITY

Based on the concept of sensory inhibition, the application of the antimuscarinics is more extensive. Several clinical trials have shown the safety and efficacy of antimuscarinics in the treatment of OAB patients with benign prostate hyperplasia. Kaplan et al [5] reported that treatment with tolterodine extended release and together with tamsulosin provides benefit for men with moderate to severe lower urinary tract symptoms including OAB. Male patients with benign prostate hyperplasia could benefit from tolterodine as a way of reducing urgency, urgent incontinence, frequency and nocturia [5,6]. Generally speaking, the use of antimuscarinics in OAB patients should improve

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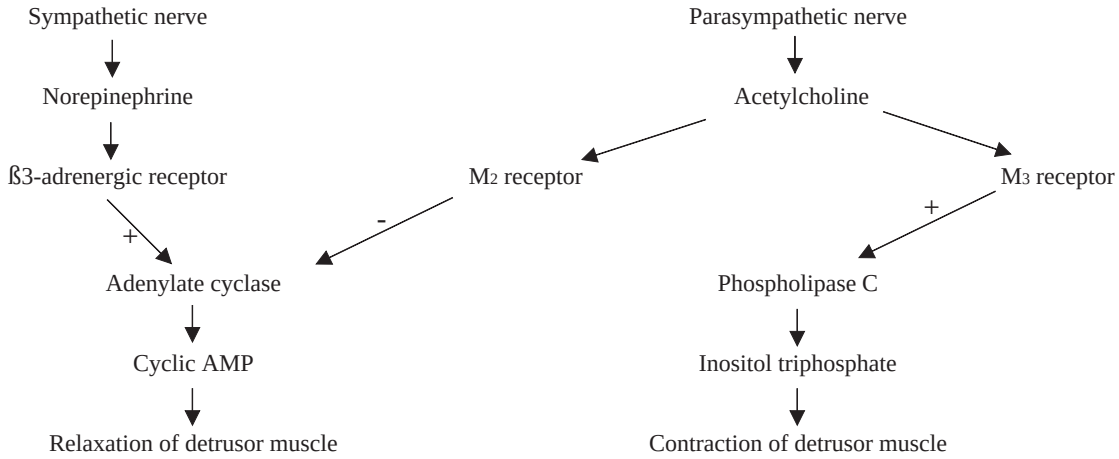

Fig. 1. Current concepts of the autonomic efferent pathways contributing to detrusor contraction.

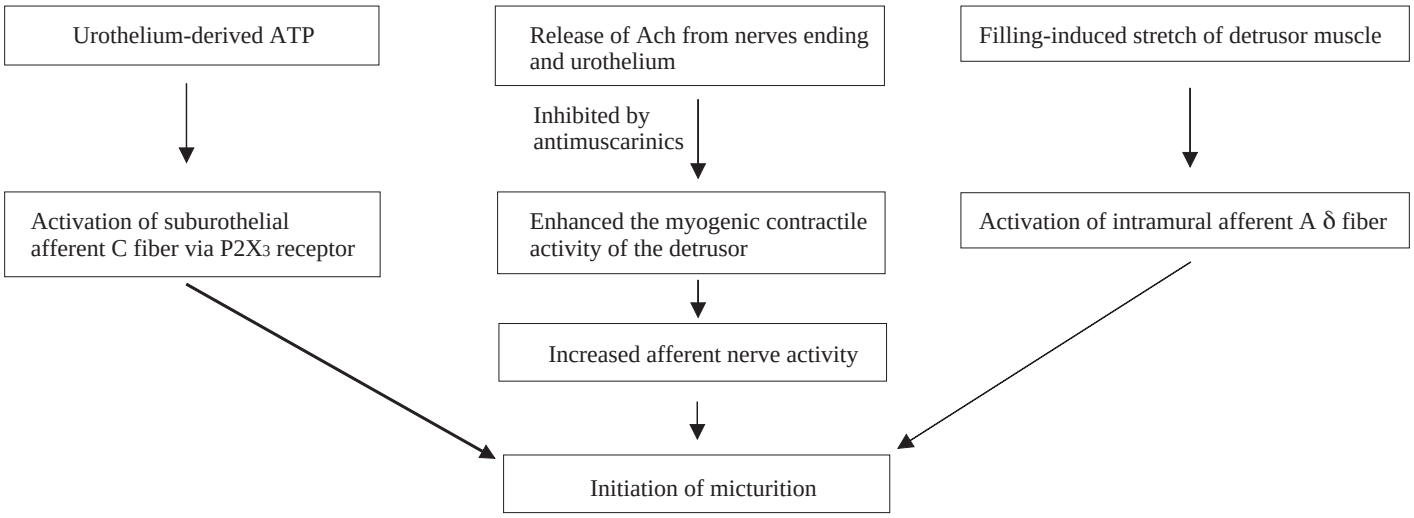

Fig. 2. The effect of antimuscarinics on the storage phase of bladder activity.

functional voiding capacity and maximum bladder capacity significantly, but without decreasing the maximum uroflow rate [7]. However, it should be noted that men who suffered from severe bladder outlet obstruction should avoid the use of antimuscarinics.

In the treatment of neurogenic detrusor overactivity, botulinum toxin has been shown to have advantages in short and long term effects on patients with refractory spasmodic neurogenic bladder [8,9]. However, a recent study showed that using two kinds of high-dosage antimuscarinic medications, a large proportion of patients who had previously demonstrated an unsatisfactory outcome with dosage-escalated monotherapy, could now be treated successfully [10]. The appearance of side effects was comparable to that found with normal-doses of antimuscarinics. Antimuscarinic drugs that have a mixed action in the treatment of detrusor overactivity, blockade of voltage-gate calcium-ion channels and local anesthesia have been reported [3]. For example, oxybutynin has both an antimuscarinic and a direct muscle-relaxant effect as well as acting as a local anesthesia. Propiverine combines antimuscarinic and calcium antagonistic activity. To choose the appropriate antimuscarinic, reports from evidence-based clinical trials are important.

THE RATIONALE OF USING ANTIMUSCARINICS IN OVERACTIVE BLADDER

The available data may be considered promising and the use of antimuscarinics has been demonstrated to be quite safe treatment for OAB. Nonetheless, patients with a potential risk of detrusor underactivity should be treated with antimuscarinics in a very careful manner. Uroflowmetry and postvoid residual volume estimates are essential in the evaluation of patients with OAB, although urodynamic endpoints are not an adequate method of predicting symptom improvement in OAB. For patients with neurogenic disturbance, the aim of the treatment is to prevent high intravesical pressures and to protect the upper urinary tract. Improvements in the patient's quality of life and lower urinary tract symptoms are the clinical value of using antimuscarinics for the treatment of OAB.

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