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Review

New developments in the medical management of overactive bladder

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ABSTRACT

Overactive bladder (OAB) is a clinical syndrome describing the symptom complex of urgency, with or without urgency incontinence and is usually associated with frequency and nocturia. Whilst the majority of women will benefit from initial management with conservative and behavioural intervention a significant number will require medical therapy. Antimuscarinics are currently the most widely prescribed drugs for OAB although very often persistence with medication is limited due to lack of efficacy or intolerable adverse effects.

The review, whilst giving a brief overview of OAB syndrome, will focus on new developments in drug therapy for OAB. In addition to evaluating new drugs with different methods of action it will also specifically focus on alternative modalities of treatment and how they may benefit patients with this troublesome and distressing condition.

Contents

1. Introduction

Overactive bladder (OAB) is the term used to describe the symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1].

Antimuscarinic drug therapy is often associated with poor compliance and persistence with therapy although the introduction of new medications with differing modes of action may improve efficacy whilst reducing the incidence of adverse events.

The aim of this review is to examine the current challenges in the treatment of patients with OAB as well as to provide an overview

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of the new developments in the medical management of the condition.

2. Prevalence of OAB

OAB is a common and troublesome condition which, although not life threatening, is known to have a significant impact on Quality of Life (QoL). Epidemiological studies from North America have reported a prevalence of OAB in women of 16.9% and the prevalence increases with age rising to 30.9% in those over the age of 65 years [2]. Further prevalence data from Europe [3] also has shown the overall prevalence in men and women over the age of 40 years to be 16.6%. Frequency was the most commonly reported symptom (85%) whilst 54% complained of urgency and 36% urgency incontinence.

3. Pathophysiology of OAB

The symptoms of OAB are thought to be due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [4]. However OAB is not synonymous with detrusor overactivity as the former is a symptom based diagnosis whilst the latter is a urodynamic diagnosis [5]. It has been estimated that 64% of patients with OAB have urodynamically proven detrusor overactivity and that 83% of patients with detrusor overactivity have symptoms suggestive of OAB [6].

4. What are the challenges in current OAB management?

Persistence with medication remains a problem across many different chronic disease states although the evidence would suggest that compliance with antimuscarinic therapy tends to be lower than other chronic health problems such as osteoporosis, hypertension and diabetes [7]. Historically compliance with immediate release preparations has been reported to be low [8] with only 18% of patients continuing therapy at 6 months. This has not substantially improved despite the introduction of long acting slow release preparations and more efficacious bladder selective drugs. A recent retrospective analysis of antimuscarinic prescribing in the UK has shown persistence rates at 12 months to range from 14% to 35% with little difference noted between the different medications [9].

The reasons why compliance and persistence with OAB therapy remain poor is generally considered to be due to lack of efficacy or because of the troublesome side effects associated with antimuscarinics such as dry mouth, constipation, blurred vision and somulence [10]. Consequently improving efficacy and tolerability may lead to an improvement in terms of patient acceptability and therefore compliance.

5. Alternative delivery mechanisms

Alternative delivery mechanisms may offer increased tolerability and patient acceptability whilst maintaining efficacy. Transdermal oxybutynin has been compared with tolterodine ER in 361 patients with mixed urinary incontinence. Both agents significantly reduced incontinence episodes, increased volume voided and led to an improvement in quality of life when compared to placebo. The most common adverse event in the oxybutynin patch arm was application site pruritus in 14% although the incidence of dry mouth was reduced to 4.1% compared to 7.3% in the tolterodine arm [11].

Whilst transdermal oxybutynin is effective in reducing the number of adverse effects related with antimuscarinic therapy it may be associated with significant skin site reactions. More recently the use of oxybutynin topical gel has been investigated in a large North American multicentre randomised, placebo controlled study of 789 patients with OAB [12]. Overall oxybutynin gel was associated with a significant decrease in urge incontinence episodes and urinary frequency when compared to placebo with a corresponding increase in voided volume. Dry mouth was higher in the oxybutynin arm than the placebo arm (6.9% vs 2.8% respectively) as were skin site reactions (5.4% vs 1.0% respectively) although would appear to be lower than those associated with the patch. These findings are also supported by a further 12-week placebo controlled study investigating the use of oxybutynin gel in women with OAB. Overall there was a significant reduction in incontinence episodes and frequency with a corresponding improvement in Quality of Life (QoL). Dry mouth was higher in the oxybutynin gel arm when compared to placebo (7.4% vs 2.8%; $p = 0.0062$) although was considerably lower than rates seen with oral medication [13].

Whilst the transdermal approach has been associated with similar efficacy and a reduction in adverse events skins site reactions remain troublesome. More recently the efficacy and safety of an oxybutynin vaginal ring has been assessed in a large multicentre, randomised double blind placebo controlled trial of 719 women. Overall those women using the oxybutynin vaginal ring (4 mg and 6 mg) demonstrated a greater reduction in incontinence episodes and micturition frequency when compared to placebo. Dry mouth rates were 2.6%, 4.9% and 10.2% in the placebo arm, the 4 mg group and the 6 mg group respectively. Constipation rates were reported as <5% [14].

Consequently alternative routes of administration may offer a more favourable balance of reduced adverse effects and are alternatives to oral preparations in those women who suffer with intolerable antimuscarinic adverse effects.

6. New developments in drug therapy

6.1. Calcium antagonists

Contractile activity in the bladder smooth muscle is activated by the movement of extracellular calcium into the cell. The inhibition of the entrance of Ca^{2+} can prevent spontaneous and evoked contractile activity [15] with L-Type Ca^{2+} blocking agents, such as nifedipine, inhibiting the entry of extracellular calcium.

Nifedipine has been shown to reduce the frequency and amplitude of detrusor contractions [16] although these findings have not been confirmed in a further study which found there was no significant effect [17]. Similar contradictory findings have been reported regarding the use of flunarizine [18]. Diltiazem has also been shown to significantly increase bladder capacity, lower bladder pressure and decrease the number of episodes of incontinence [19].

Whilst the evidence would support an effect on the bladder at present there is insufficient evidence to suggest that calcium channel blocking agents are effective in the treatment of detrusor overactivity.

6.2. Potassium channel opening agents

The opening of K^+ ion channels in the membrane of the detrusor muscle cell results in an increase in K^+ movement out of the cell resulting in membrane hyperpolarization [20] This reduces the opening probability of ion channels involved in membrane depolarization and hence excitability is reduced [21]. Potassium channel openers are thought to be active during the bladder filling phase and, whilst abolishing spontaneous detrusor contractions, are not thought to affect normal bladder contractions. However, their clinical usefulness is limited by significant cardiovascular effects, with cromakalim and pinacidil being found to be up to 200