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The Evidence for Antimuscarinic Agents in Female Mixed Urinary Incontinence

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Abstract

Antimuscarinic agents are the most commonly used treatments for overactive bladder (OAB) syndrome where they reduce urgency, frequency, and urge incontinence. Despite few studies investigating the effects of antimuscarinic agents on mixed urinary incontinence (MUI), awareness is increasing about their value as first-line treatments for patients with MUI (combination of OAB wet and stress urinary incontinence). Evidence suggests that they are as effective in patients with urgency-predominant MUI as they are in OAB, resulting in significant reductions in urgency episodes, urinary frequency, and incontinence.

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1. Background

Antimuscarinic agents are the most commonly used treatments for overactive bladder (OAB) syndrome. They reduce urgency, frequency, and urgency incontinence through antagonistic effects at the muscarinic (M2 and M3) receptors on the detrusor muscle of the bladder [1].

As previously described, mixed urinary incontinence (MUI) is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing [2]. In effect, it is a combination of OAB wet and stress urinary incontinence (SUI).

The treatment of MUI has traditionally focused on the pathophysiology of the predominant symptoms. This has included physiotherapy and surgery for SUI and bladder retraining and pharmacotherapy to address the OAB. Within this latter category, evidence supports the use of antimuscarinic agents in MUI as well as in OAB.

To verify this, a search of the medical literature was conducted using PubMed and Embase to access English-language citations contained in Current Contents/All Editions and MEDLINE through August 2006. The search terms "women and urinary mixed incontinence, pharmacological therapy" were used to identify relevant papers from peer-reviewed journals.

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2. The role of antimuscarinic agents

Despite the significant prevalence of MUI and its considerable impact on quality of life, few studies have investigated the effects of antimuscarinic agents specifically on this condition. Most have considered subgroups of patients with MUI within studies of OAB.

In 1989, Karram and Bhatia reported data on 52 patients with objective evidence of combined stress and urgency incontinence, 27 of whom were treated primarily with retropubic urethropexy (modified Burch procedure) and 25 medically with oxybutynin, imipramine, and oestrogen [3]. Thirty-two percent of those treated medically were cured and 28% were markedly improved, compared with 59% and 22%, respectively, of those who had surgical treatment. Urodynamic evaluation had no predictive value for cure or improvement. There was no statistically significant difference between the two treatments, and the researchers concluded that patients with combined SUI and detrusor overactivity should initially be managed medically to reduce the incidence of surgical intervention.

More recently Dmochowski et al. reported a significant reduction in the number of weekly incontinence episodes using 3.9 mg transdermal oxybutynin compared to placebo (median change −19.0 vs. −14.5 [$p = 0.0165$]) in a group of 520 adults with OAB and urge urinary incontinence (UUI) or MUI [4]. Dmochowski et al. consistently showed a comparable efficacy of 3.9 mg/d transdermal oxybutynin and 4 mg/d long-acting tolterodine in reducing the number of daily incontinence episodes, which was significantly better than placebo ($p < 0.05$), in a population of 361 adults with UUI and MUI [5].

3. Tolterodine

In the first study to look specifically at patients with MUI, 60% of 410 women who were treated for 8 wk with slow-release tolterodine had a regression in symptoms [6].

In a subsequent study of 239 patients with urgency-predominant MUI and 755 patients with UUI alone, treated with tolterodine 1 or 2 mg twice daily for 16 wk, the median reduction in incontinence episodes from baseline was 67% in the patients with MUI and 75% in those with UUI [7]. Thirty-nine percent of the patients with MUI and 44% of those with UUI were dry at the end of the study, and neither of the differences in effectiveness between the MUI and UUI groups was statistically significant. The authors concluded that tolterodine was as effective at reducing urinary leakage and other OAB symptoms in patients with MUI as it was in those with UUI. On this basis, antimuscarinic treatment could be considered an effective first-line treatment option for patients with urgency-predominant MUI.

The first prospective, randomised trial to look specifically at patients with MUI was the Mixed Incontinence Effectiveness Research: Investigating Tolterodine (MERIT) study, which included 854 women with urgency-predominant MUI [8]. Patients were recruited if they had UUI (five or more episodes per week), urinary frequency (eight or more micturitions on average per 24 h), and urgency (a strong and sudden desire to void) in combination with SUI.

Subjects received 4 mg extended-release tolterodine or placebo, once daily for 8 wk. Patients in the two treatment groups were well matched for age and symptom severity. At baseline, patients in the placebo group experienced a mean of 21.4 episodes of UUI per week and 9.7 episodes of SUI. This compared with 20.7 and 9.2 episodes in the tolterodine group.

After 8 wk of treatment, mixed incontinence episodes were reduced by a median 50.6% in the placebo group compared with 72.9% in the tolterodine group ($p < 0.01$). Urinary frequency was reduced by a median 13.8% and 20%, respectively ($p < 0.01$). Urgency episodes were reduced by a median 19.2% in the placebo and by 37.2% in the tolterodine group ($p < 0.001$).

Outcome was not affected by whether patients had experienced first SUI or first UUI. This was in contrast to a previous study of surgery in MUI that showed that operations were more likely to be successful when SUI rather than UUI had been the first symptom [9].

The reduction in weekly urgency incontinence episodes was comparable to that previously reported with extended-release tolterodine 4 mg/d in a 12-wk study of patients with OAB [10], leading the MERIT authors to conclude that the ability to treat UUI was unaffected by the presence of SUI [8]. They recommended that, because UUI has a greater negative impact on quality of life, ''treating the urgency component first would seem justified in women in whom urgency and stress incontinence episodes occur with equal frequency.''

In 2250 patients with OAB symptoms with concomitant SUI treated with 2 mg tolterodine twice daily for 12 wk, Michel et al. showed that severity of SUI (defined as 1–3 degrees according

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