The safety and efficacy of tolterodine extended release in the treatment of overactive bladder in the elderly

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Abstract: After lifestyle and behavioral measures to control overactive bladder, the mainstay of pharmacological treatment is the use of antimuscarinic therapy. Overactive bladder predominantly affects older people, who experience the most severe disease, and are also at a greater risk of side effects from antimuscarinic therapy. Thus it is imperative that data are available on the efficacy and tolerability of this group of drugs when used in older people. This article reviews the pathophysiology of the condition, its effect on the elderly and the evidence for the use of extended release tolterodine in the elderly using data from placebo and active drug controlled studies.

Keywords: overactive bladder, tolterodine, urgency incontinence

Introduction

Overactive bladder (OAB) is chronic debilitating disorder characterized by the symptoms of urinary urgency with or without urgency incontinence, usually accompanied by frequency and nocturia in the absence of infection or other obvious pathology.[1] These symptoms may result from over activity of the bladder detrusor muscle, spontaneous, unprovoked contractions of the detrusor causing urgency or, alternatively, it may occur with urethro-vesical dysfunction. Additionally, there has been increasing interest in the sensory pathway from the bladder and the role of the urothelium in mediating urgency the pathophysiology of the condition over the past few years.[2] Although the condition affects all ages, the prevalence of this condition increases with increasing age. In a European and Canadian study the prevalence of OAB was estimated as 16.6% in people of 40 years or older, with nocturia and urinary urgency being the most commonly reported symptoms.[3]

For the majority of patients with OAB the underlying etiology remains unknown. However, recognized associations include: neurological impairment (multiple sclerosis, spinal cord injury), neurological degeneration (Parkinson's disease, multi-system atrophy) and bladder outflow tract obstruction.[4,5] OAB can be socially disabling and it can have a profound effect on the quality of life of individuals, which appears to be greater than stress urinary incontinence, which may be related to the unpredictability of the symptoms.[6–8] Low self-esteem and embarrassment occur and patients may withdraw from social activities and become depressed.[9,10] Urgency incontinence is associated with an increase in the number of falls and fracture in the elderly population.[9] Unfortunately, there is a widespread misconception among patients and healthcare providers that the symptoms of OAB are due the effects of aging and are an inevitable process about which little can be done. This misunderstanding leads to a delay in people seeking treatment for their symptoms and to clinicians failing to treat patients either seriously or at all, prolonging the suffering associated with the condition.

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Some data suggest that within the population, older people may experience the most severe disease compared with the young.[12] Unfortunately, the portion of the population in which the prevalence of the condition is highest is probably less likely to receive active treatment for their condition; this is most marked in those who reside in institutional care, where under-use is well recognized.

Basis of treatment

The treatment of individuals with OAB involves behavioral, pharmacological and surgical interventions which are applied according to disease severity and symptom response. Behavioral treatment regimes rely on motivated, agile individuals with good cognition but the elderly are not precluded from bladder-retraining regimens. It is thought likely that, because of their reduced ability to hold on in the face of urgency the elderly do not do as well with bladder retraining as a sole intervention.[10]

Pharmacological treatments have to date focused on targeting the parasympathetic system which controls motor activity and modulates active bladder relaxation during filling, acting via cholinergic muscarinic receptors. Muscarinic receptors can be classified into 5 subtypes.[11] Studies have demonstrated that in the human, the detrusor muscle predominantly contains muscarinic receptors of the M2 and M3 subtypes.[15] In health, the motor innervation to the bladder is wholly dependent on the action of acetylcholine acting via M3 receptors, although this changes in disease states.

Continence is achieved during the urine storage phase by inhibition of the parasympathetic nervous system and concurrent activation of the sympathetic nervous system. This results in bladder relaxation with co-existent contraction of the urethral sphincter. When bladder capacity is reached, the pontine micturition center acts as the switch between storage and voiding and causes inhibition of the sympathetic system and activates the parasympathetic system, resulting in relaxation of the urethral sphincter and a sustained bladder contraction. The spontaneous contractions of the detrusor, while attempting to inhibit micturition thought to be the origin of symptoms of urinary frequency and urgency during urine storage, are thus the target of current drug therapy.

Anti-muscarinic agents such as oxybutynin, tolterodine, propiverine, trospium, solifenacin, darifenacin and fesoterodine have thus been developed for the treatment of OAB. Although extensive work has been conducted to assess the efficacy and safety of anti-muscarinics in patients with OAB, the majority of studies have focused on a relatively young patient population and none have reported results stratified by age. This review addresses the evidence for the safety and efficacy of anti-muscarinics in the elderly population, concentrating upon tolterodine extended release. Other articles have reviewed care for the incontinent elderly and other specific treatments, but are outside the scope of this article.[12–14]

Oxbutynin

Oxybutynin immediate release (Oxy-IR) has proven efficacy for the condition but it has a significant incidence of anti-muscarinic side effects such as dry mouth, constipation, blurred vision and central nervous system side effects. Withdrawal from treatment is a significant problem, and in one observational study only 18% of subjects (women) remained on active treatment 6 months following the initial prescription.[15] Of particular concern the effects on the central nervous system (CNS) are worrying, and cognitive impairment has been noted with oxybutynin.[17,18] Oybutynin is a relatively small tertiary amine with a high lipophilicity, enabling it to penetrate the blood–brain barrier and affect the CNS.[16] Oxy-IR is primarily metabolized by the cytochrome P-450 system primarily in the liver and the upper gastrointestinal tract, resulting in the production of the metabolite N-desethyloxybutynin. The active metabolite of Oxy-IR, N-desethyloxybutynin, appears to contribute to some of the adverse effects, particularly dry mouth, as it acts as a competitive antagonist against muscarinic receptors in human detrusor muscle and it is present in serum at higher dose than the parent compound.[17] To reduce the side effect profile of Oxy-IR an extended release[18] and subsequently a transdermal preparation were developed.[19] Oxybutynin extended release is primarily absorbed in the colon where there is no cytochrome P-450 system to metabolize it thus limiting metabolite production, improving bioavailability and an improved side effect profile. Likewise, the transdermal preparation avoids the first pass metabolism of oxybutynin, reducing the formation of the active metabolite with an associated reduction in the incidence of typical antimuscarinic side effects.[20]

Tolterodine

Tolterodine (Tolt-IR) is an established muscarinic antagonist effective in the treatment of OAB. Unlike oxybutynin, data from animal studies suggest that tolterodine, although a non-selective antimuscarinic agent, exhibits preferential organ specific selectivity to M2 and M3 muscarinic receptors found in the bladder, accounting for an improved side effect profile with respect to the occurrence of dry mouth.[21] In a study of alpha wave suppression on the EEG, Tolt-IR

did not have a significant electrophysiological effect when compared to oxybutynin.[16] Studies have shown that Tolt-IR had a comparable efficacy to Oxy-IR but it is considerably better tolerated.[22,23] The safety and efficacy of Tolt-IR in older patients has been specifically examined. The first, a multi-national, phase 3, randomized, double-blind placebo-controlled, parallel group study lasting 4 weeks recruited 177 patients aged 65 and older (115 women, 62 men [mean age 75, range 62–92]). Subjects with urgency, urinary frequency (≥8 micturutions per 24 hours), and/or urgency incontinence (≥1 urgency incontinence episode per 24 hours) as determined by micturition diaries were eligible for inclusion. The study randomized patients in the ratio of 3:3:2 to Tolt-IR 1 or 2 mg or placebo respectively. There were no clinically relevant changes between the three treatment groups in ECG variables or morphology or in laboratory parameters. The tolterodine was well tolerated with 87% of subjects taking Tolt-IR 1 mg bd, 87% of Tolt-IR 2 mg bd completing the study compared with 91% of those on placebo. Subjects enrolled in the study were encouraged to report adverse events. Dry mouth was the only adverse event that occurred significantly more often in patients treated with Tolt-IR (1 mg bd, 30% 2 mg bd, 48%) in comparison to the placebo group (9%). The majority of instances of dry mouth were mild and moderate in intensity. Three percent of Tolt-IR treated subjects withdrew from treatment because of dry mouth, compared to 2% of placebo-treated subjects. No subject developed acute urinary retention, a side effect of considerable concern with anti-muscarinic treatment and CNS adverse effects did not occur more frequently in Tolt-IR treated patients.

Tolt-IR 2 mg bd was more efficacious than placebo in improving micturition variables. There was a statistically significant reduction in both the number of micturtions per 24 hours (mean reduction –0.7 95% CI –1.1 to –1.3, $p = 0.0001$) and the number of urgency incontinence episodes per 24 hours (mean reduction –0.7 95% CI –1.3 to –0.2, $p = 0.0074$) compared to baseline. The volume voided per micturition was significantly greater (mean +16 mL, 95% CI, 5–30 mL, $p = 0.0099$). The mean reduction in incontinence episodes and increase in volume voided per micturition were not statistically significantly different for subjects taking Tolt-IR 1 mg bd. The findings from this particular study suggest that Tolt-IR was an effective and safe drug in the treatment of OAB in older patients at a dose of 2 mg bd and was consistent with the recommended dosage of Tolt-IR.[24] The clinical relevance of these findings is, however, questionable. The study was extremely short in its design and there were no quality of life data by which the clinical relevance of the findings might be judged. In addition, the number of subjects was small and they were most likely drawn from a population of "fitter" elderly. No stratification of effect by age was presented. This study was, however, in its time, a significant advance in knowledge of the effect of these drugs in older people.

Tolterodine extended release

The development of tolterodine extended release (Tolt-ER), a capsule formation that provides a sustained release over 24 hours, allowed a once-daily dosing regime. Given the relatively low adherence to anti-muscarinics this was thought to provide an advantage and would be more convenient to patients. Importantly once-daily dosing may be of particular benefit to older patients in whom adherence to more complex drug regimens may be more difficult. Once-daily dosing is also easier to achieve for statutory services administering medication to older frailer people at home. When compared to Tolt-IR and placebo in a randomized controlled clinical trial of 1529 adult subjects (80% female, mean age 60, range 20–93) with OAB over 12 weeks,[25] both Tolt-IR and Tolt-ER were associated with statistically significant reductions in the primary efficacy variable in the study, the number of incontinence episodes per week, compared with placebo ($–6.9 \pm 15.4$), Tolt-ER ($–11.8 \pm 17.8$, $p = 0.0001$) Tolt-IR ($–10.6 \pm 16.9$, $p = 0.0005$). When the median percentage change from baseline in weekly incontinence episodes associated with Tolt-ER was compared with that associated with Tolt-IR, Tolt-ER was found to be more effective (Tolt-ER 71%, Tolt-IR 60%, $p < 0.05$). The reduction in incontinence episodes was accompanied by a reduction in pad usage to one pad daily, a 36% reduction from baseline in both groups, significantly different from placebo ($p < 0.02$ for each group). When adverse events in the treatment groups were analyzed, only dry mouth was observed at an increased frequency in the patients treated with tolterodine in comparison to placebo. Patients treated with Tolt-ER had 23% less dry mouth than those treated with Tolt-IR ($p < 0.02$). Most instances of dry mouth were reported as mild or moderate; only 1.8% of those treated with Tolt-ER experienced a severe dry mouth. There were no cardiovascular and CNS concerns, suggesting that this drug might also be efficacious in older people.

A comparison of the older (>65 years) and younger (<65 years) groups from the same study, which addressed the efficacy, safety and tolerability of Tolt-ER, found a comparable reduction in incontinence episodes per week between the younger (mean reduction –12.0, SD 17.6)

subjects and those >65 years (mean reduction 11.5, SD 18.2). Both groups of subjects experienced a statistically significant increase in volume voided per micturition compared to placebo (young 35 mL (SD, 33 mL), older 33 mL, SD 47 mL). Whereas the Tolt-ER treated subjects <65 years experienced a significant reduction in micturition frequency versus placebo, no difference was observed in the older group. In an examination of the response to urgency – assessing the subject's ability to finish tasks before voiding –26.2% of older subjects treated with Tolt-ER 4 mg experienced an improvement in this ability versus 14.8% on placebo ($p < 0.003$). After 12 weeks, 69.8% of older Tolt-ER -treated subjects considered their treatment to be of benefit, versus 46.9% of those on placebo ($p < 0.001$), significantly fewer than the younger Tolt-ER treated group. Younger patients also reported a statistically significantly greater response to placebo treatment than did the older placebo-treated group, and thus there was no difference in a between-age group analysis of proportionate benefit attributable to Tolt-ER versus placebo ($p = 0.69$). Following an analysis of safety in subjects receiving at least one dose of study medication in 291 younger and 214 older subjects, the most common adverse events were dry mouth (22.7% young versus 24.3% older), headache (8.3% young versus 3.7%, older) and constipation (5.9% young versus 6.1% older). The majority of instances of dry mouth in the older group were mild or moderate, with severe dry mouth reported in 1.9% (versus 1.7% in younger subjects). Headache occurred statistically significantly more frequently in tolterodine treated subjects younger than 65 years of age ($p = 0.04$). There was one case of voiding difficulty in a male subject which resulted in withdrawal from the study but no cases of acute urinary retention. Six older subjects withdrew because of lack of efficacy. CNS adverse effects did not occur at a greater rate in subjects older than 65 years of age.[25] Overall, Tolt-ER was efficacious and well tolerated in the older group of subjects. Of note in this study was the lesser (non-drug), placebo response in older subjects. This may, as noted by the authors, be due to an effect of medical co-morbidities negating this effect but may be also due to the fact that older people experience more severe disease than younger people,[12] who may therefore be less likely to respond to non-drug intervention.

In terms of quality of life, the longer-term impact of Tolt-ER has been examined in two studies including older people.[26,27] There are, once again, no age-stratified data yet available or any specific studies examining the impact of treatment in older people. In the first, data from a 12-week randomized controlled trial of Tolt-ER were analyzed using the King's Health Questionnaire (KHQ) and the Medical Outcomes Study Short Form 36-item questionnaire (SF-36). Subjects also rated their bladder condition in terms of self-perceived control. Assessments were performed at baseline and at the end of treatment. At end of treatment, KHQ domains selected a primary end points (incontinence impact and role limitations) significantly improved ($p \leq 0.001$) with Tolt-ER. Secondary end point domains (physical limitations, sleep and energy, severity [coping] measures, and symptom severity) were also significantly improved ($p \leq 0.006$) after treatment with Tolt-ER. The Tolt-ER group had decreased symptom severity and statistically significant improvements in patient rating of bladder control compared with the placebo group at end of treatment. No treatment differences were detected using the SF-36. In the second, related study, KHQ data were analyzed from a group of subjects completing a 12-week randomized controlled phase followed by an open-label follow up for a year in incontinent OAB sufferers. Data were available for 838 subjects (mean age, 61.1 years; 80.9% women). The KHQ, significantly and clinically improved from baseline to months 3 and 12 on all domains apart from general health perception. Improvements were consistent for the 3- and 12-month time frames.

The effect of tolterodine on cognitive function in otherwise healthy, cognitively intact older people has been assessed, but results are only available as an abstract.[28] This study, of identical design to those used to assess darifenacin, a M3 specific antimuscarinic for OAB,[29] found that there was no detectable difference in the primary end point, delayed face-name recall, between a single dose of Tolt-ER 4 mg and Oxy-ER 15 mg. However, there was, in this study, and in contrast to previous studies, no detectable effect attributable to oxybutynin.

Tolterodine compared with other drugs

Tolterodine has been the active comparator in a number of studies, which although not specifically designed for examining treatment response in older people, has included older subjects, although these would be usually drawn from the "young" elderly and would be fitter than many. We report on these for completion. Tolterodine 2 mg bd has been compared to solifenacin in a placebo-controlled 12-week study which included 34% subjects over 65 years of age. No comparison between older and younger patients was reported but tolterodine treatment reduced urinary urgency episodes per day by –2.05 from a baseline of 5.45, a difference from placebo that did not reach statistical significance ($p = 0.0511$).

There was likewise no difference between placebo and tolterodine in reduction of urgency incontinence episodes and all incontinence episodes.[30] When compared against Tolt-ER in the STAR[31] study, a double-blind, double-dummy, two-arm parallel group trial conducted over a 12-week period was analyzed for non-inferiority of solifenacin for the primary outcome measure of micturition frequency. Thirty percent of included subjects were over 65 years of age and were either treated with solifenacin 5 or 10 mg or Tolt-ER 4 mg daily. The dose of solifenacin was adjusted after 4 weeks according to subject response and request, and placebo was added to tolterodine should a dose increase be requested. After the achievement of non-inferiority on the primary end point, a conventional analysis of secondary variables was performed. Solifenacin (5 and 10 mg) was associated with a significant improvement over Tolt-ER in urinary urgency ($p = 0.035$), urgency incontinence episodes ($p = 0.001$), overall incontinence ($p = 0.006$) and reduction in pad usage ($p = 0.0023$). Moreover, 59% of solifenacin-treated subjects who were incontinent according to their 3-day diary data at the beginning of the study became continent compared with 49% of patients of patients treated with Tolt-ER ($p = 0.006$). In an analysis of the solifenacin 5 mg versus tolterodine 4 mg treated groups over the first 4 weeks of the study, solifenacin was associated with a statistically significant improvement over tolterodine in terms of reduction in incontinence episodes per 24 hours (solifenacin –1.30 versus tolterodine –0.90, $p = 0.0181$) and reduction in daily pad use (solifenacin –1.21 versus –0.80; $p = 0.0089$) but in no other variable. In terms of adverse events, patients taking solifenacin reported a slightly higher number of anti-muscarinic side effects than those taking Tolt-ER. However the number of patients discontinuing from the study in both groups due to adverse events was comparable. Tolt-ER has also been compared to Oxy-ER in a 12-week prospective placebo-controlled study of women with OAB.[32] No age stratified or comparative data were provided, but 39.5% of the women were over 65 and 15% over the age of 75. Improvements in weekly urgency urinary incontinence episodes were similar for the women who received Oxy-ER ($n = 391$) or Tolt-ER ($n = 399$). Oxybutynin was significantly more effective than tolterodine in reducing micturition frequency ($p = 0.003$), and 23.0% of women taking oxybutynin reported no episodes of urinary incontinence compared with 16.8% of women taking tolterodine ($p = 0.03$). Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. Dry mouth was more common with oxybutynin, but tolerability was otherwise comparable, including adverse events involving the CNS. These results persisted regardless of whether the women were treatment-naive or not.[33] In a trial of previously treated subjects with urgency or mixed urinary incontinence, comparing transdermal oxybutynin with placebo and tolterodine ER over 12 weeks, transdermal oxybutynin and tolterodine use resulted in equivalent reductions in the number of daily incontinence episodes, increased the average voided volume and improved quality of life versus placebo. The commonest adverse event associated with transdermal oxybutynin use was localized application site pruritis (14 versus 4% for placebo) accompanied by a low incidence of systemic anticholinergic side effects (eg, dry mouth 4.1%) compared to that occurring with tolterodine (7.3% versus 1.7% with placebo).[34]

In most OAB studies, men are in the minority, and most reports are of samples which are approximately 80% female. Only in the last 2 to 3 years has there been a specific attempt to examine the treatment of OAB in men. With due regard to the perceived risk of precipitating acute urinary retention in men, studies to date have used combination therapy with alpha-adrenergic antagonists to address this problem. However, once again there are no reports of efficacy either specifically addressing the elderly or yet providing results that are stratified by age. For example, in a randomized, placebo-controlled 12-week study of Tolt-ER, Tolt-ER plus tamsulosin and placebo,[35] only 23.7% of the 879 subjects were over the age of 65 years. A total of 172 men (80%) receiving Tolt-ER plus tamsulosin reported treatment benefit by week 12 compared with 132 patients (62%) receiving placebo ($p < 0.001$), 146 (71%) receiving tamsulosin ($p = 0.06$ versus placebo), or 135 (65%) receiving tolterodine ER ($p = 0.48$ versus placebo). The combination treatment performed better than tolterodine alone in relieving symptoms of OAB and in producing significant improvements on the total International Prostate Symptom Score (−8.02 versus placebo, −6.19, $p = 0.003$) and the single quality of life item (−1.61 versus −1.17, $p = 0.003$).

A small randomized, uncontrolled open trial of tolterodine 2 mg bd in combination with topical estrogen versus tolterodine alone for OAB in post-menopausal women showed, in a between-group analysis, significant improvements in mean daytime frequency and voided volume and statistically significant differences in improvement in quality of life as measured by the UDI-6 and IIQ-7 after treatment with the combination.[36]

In conclusion, from what data are available specifically for the elderly, tolterodine appears to be efficacious in

terms of a reduction in objective disease-related variables (urinary frequency, urinary urgency episodes and incontinence episodes) and appears to improve quality of life for people with the condition, although this is difficult to judge with limited data. The magnitude of efficacy equals that in younger subjects for most of these variables. Where tolterodine was compared with other active comparators, no data have been reported on efficacy in the elderly. Where studies have included a significant proportion of older subjects, there has been a statistically significantly greater improvement in symptoms with either Oxy-ER or solifenacin. However, these differences are most often small and the absolute effect size is small. Tolterodine therefore remains an effective and well tolerated management option for older people with OAB.

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