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EXPERT REVIEW

OAB Update: Focus on Trospium

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Abstract: Muscarinic receptor antagonists form the mainstay of pharmacologic therapy for overactive bladder (OAB), a prevalent, debilitating, and costly condition. Antimuscarinics differ in their specificity for certain muscarinic receptors, their metabolism, and their ability to cross the blood-brain barrier. Trospium chloride is the only antimuscarinic that is a quarternary amine and its positive charge prevents the crossing of the blood-brain barrier, thus minimizing CNS side effects. Level I evidence supports the efficacy and tolerability of both the immediate-release and extended-release formulations of trospium. Furthermore, subanalyses of data pooled from large randomized, controlled trials support the efficacy is subpopulations such as men, the obese, and the elderly. The adverse event profile is favorable, with dry mouth and constipation presenting as the main adverse sequelae. As expected, CNS side effects have been rare and cognition does not appear to be impaired in those patients taking multiple medications.

Keywords: overactive bladder, urgency incontinence, antimuscarinic, trospium chloride

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Introduction

The recent International Urogynecological Association/International Continence Society joint report on terminology defined overactive bladder (OAB) as "urgency, with or without urge incontinence, usually with frequency and nocturia."[1] The National Overactive Bladder Evaluation (NOBLE) study estimated an overall OAB prevalence may exceed 16% and, in the U.S. alone, these numbers correspond to approximately 33 million adults with OAB.[2] The authors found that in relation to chronic health disorders such as diabetes, heart disease, and asthma, OAB was only second to arthritic symptoms in terms of overall prevalence.[2] The impact of OAB on quality of life (QoL) is likewise significant. In subanalyses of the EPIC study, patients with lower urinary tract symptoms (LUTS) reported significantly greater symptom bother, worse health-related QoL (HRQoL), higher rates of depression, decreased enjoyment of sexual activity, and decreased work productivity than other subgroups.[3,4] Additionally, the prevalence of falls, fractures, and other comorbidities was significantly higher for patients with OAB than for those without OAB.[5,6]

The economic impact of OAB diagnosis and treatment is enormous. A subanalysis of the NOBLE study estimated the total cost of urinary incontinence and OAB to be $19.5 billion and $12.6 billion in year 2000 dollars, respectively.[7] As the population is aging rapidly, these numbers are only going to increase. Owing to the significant prevalence, impact on QoL, and cost to society, OAB treatment is in the forefront of healthcare today. In addition to behavioral modifications and pelvic floor physiotherapy, pharmacologic therapy in the form of muscarinic receptor antagonists is a mainstay of OAB treatment. While all available medications in this class share their target of action, they differ in receptor specificity, mode of administration, and side-effect profiles. The objective of this review is to review the background behind OAB therapy with antimuscarinic medications, with an emphasis on trospium chloride. A MEDLINE search was performed for articles either written in English or ones that could be translated using GOOGLE translator. The key words applied to the search were: overactive bladder, anticholinergics, and trospium. As trospium chloride is a relatively new addition to the muscarinic receptor antagonist group in the U.S., but there is a significant amount of data from earlier European trials, no time-frame was imposed on the literature search.

Pathophysiology of OAB

Normal physiological adaptations during the storage of urine require coordination between the bladder body and outlet, which are innervated by three sets of peripheral nerves.[8] Efferent axons in the sympathetic and parasympathetic nerves modulate the contraction and relaxation of smooth muscle in the detrusor and bladder outlet, while the somatic nervous system controls the external urethral sphincter and pelvic floor musculature. Urinary storage is achieved primarily by spinal reflex pathways under the control of the brainstem. Increased wall tension during bladder filling activates bladder afferent nerves, which reflexively activate sympathetic outflow to the lower urinary tract from the lumbosacral spinal cord.[9,10] As a result, the hypogastric nerve causes internal sphincter contraction and ganglionic inhibition, while the pudendal nerve causes contraction of the external sphincter and pelvic floor striated musculature. The sacral parasympathetic outflow is typically inactive during the storage phase. The end result is detrusor inhibition and outlet excitation, resulting in continent, low-pressure storage of urine.

Symptoms of OAB such as urgency and urgency urinary incontinence (UUI) are frequently associated with detrusor overactivity (DO), urodynamic evidence of involuntary detrusor contractions during bladder filling.[1,11] The development of DO is complex and likely multifactorial, with hormonal changes, bladder outlet obstruction (BOO), aging, ischemia, and concomitant neurologic conditions thought to be contributing factors.[12] Historically, DO was thought to result from a decreased capacity of the bladder to handle increased afferent information or from a decrease in tonic inhibition of afferent impulses.[13] Bladder contractions often seen during normal bladder filling may be suppressed with a voluntary increase in suprapontine inhibition; however, suprapontine inhibition may be impaired in conditions such as stroke. As a result, involuntary detrusor contractions may be generated from low intensity afferent input and at lower bladder volumes. The "myogenic theory" postulates that conditions such as BOO, neurogenic insult, and normal aging, may also lead to morphologic changes in the detrusor resulting in progressive denervation and hypertrophy of the bladder wall.[12,14–16]

A novel cascade of peripheral events that may lead to DO and OAB is considered by many today to be the mechanism of action of antimuscarinic medications.[13] An enhanced reaction to heightened wall tension and stretching of the detrusor smooth muscle may lead to increased afferent signaling during bladder filling.[13] Additionally, increased afferent activity may result from increased urothelial signaling to suburothelial nerves, often seen in normal aging and BOO.[13] It has also been proposed that the amount of acetylcholine (Ach) released from the urothelium during bladder filling is significantly more than the typical basal Ach release.[13] The increase in Ach release from neuronal and urothelial sources increases the sensitivity of the detrusor to neurotransmitters.[13] The resultant micromotion of the detrusor increases the afferent signaling in the suburothelium and detrusor, leading to the sensation of urgency.[13]

Muscarinic receptors and their binding characteristics

Five muscarinic receptor subtypes have been identified(M1-M5) and consistent expression of M1-M3 and M5 muscarinic receptors has been found in the urothelium and lamina propria.[17,18] In humans, M2 receptors appear to outnumber the M3 receptors which mediate bladder contraction by approximately four to one.[19,20] Muscarinic receptors have been found in three locations within the urinary bladder.[19] Activation of these receptors in the detrusor smooth muscle causes contraction, while activation of urothelial receptors causes the release of a factor that inhibits detrusor contraction. Finally, activation of receptors on parasympathetic and sympathetic nerve endings influences neurotransmitter release.[19] Traditionally, it was thought that muscarinic receptor antagonists mediated their effects by blocking receptors on the detrusor muscle, thus inhibiting bladder contraction due to Ach release from parasympathetic nerves. However, at therapeutic doses, muscarinic antagonists do not appear to significantly affect bladder contractility.[21,22] Furthermore, the density of urothelial muscarinic receptors appears to be twice that found in the detrusor smooth muscle.[23] Thus, it is now accepted that muscarinic antagonists increase bladder capacity and decrease urgency mainly during bladder filling by their action at the urothelial muscarinic receptors.[13,24]

Treatment with muscarinic receptor antagonists

Antimuscarinic medications are the mainstay of pharmacologic therapy for symptoms associated with OAB. The available drugs in this class (oxybutynin, tolterodine, solifenacin, darifenacin, trospium, and fesoterodine) all block the muscarinic receptor but differ in several ways. All of the medications are available in extended-release (ER), once-daily oral preparations, while oxybutynin, tolterodine, and trospium are available in immediate-release (IR) preparations which are administered twice or thrice daily. Oxybutynin is also available in transdermal patch and gel applications, which bypass drug metabolism in the liver and may be associated with a lower incidence of adverse events (AEs). Furthermore, solifenacin and darifenacin are highly selective for the M3 receptor,[25,26] as opposed to other medications in this class which block both M2 and M3 receptors nonselectively.

The efficacy of OAB treatment with antimuscarinics has been documented in several Cochrane systematic reviews. In a summary of 61 trials that included over 11,000 patients comparing placebo and active treatment with several antimuscarinics, the authors found that cure or improvement, difference in leakage episodes per 24 hours, and difference in the number of voids in 24 hours were statistically significant favoring medication.[27] The majority of the trials were double-blinded. Another Cochrane database review provided evidence that treatment with antimuscarinic medications provided more symptomatic improvement than bladder training.[28] The combination of antimuscarinics and bladder training was also associated with more improvement than bladder training alone.

Trospium chloride IR (20 mg twice or thrice daily)

Trospium is currently the only available muscarinic receptor antagonist that is a hydrophilic, quaternary ammonium compound, which is in contrast to the other drugs in this class which are uncharged, lipophilic tertiary amines. Owing to its positive charge, trospium does not cross the blood-brain barrier which theoretically reduces the potential of central nervous system (CNS) adverse events. The absorption of trospium IR when taken with a heavy meal is reduced and may produce area under the plasma concentration-time

curve (AUC) and peak plasma concentration (C_{max}) values 70%–80% lower than those obtained while fasting.[29] The relative bioavailability of orally-administered trospium 15 mg thrice-daily tablet (with concomitant food intake) has also been compared with oral administration of a 60 mg once-daily formulation (with delayed food intake and concomitant food intake).[30] Based on the statistical analysis of the AUC representing the extent of absorption, the relative bioavailability of the IR formulation in comparison to the ER formulation was 179% (90% CI: 160%–200%) with delayed food intake and 196% (90% CI: 176%–220%) with concomitant food intake. This data indicates that higher and more homogeneous mean trospium plasma concentrations may be attained with the IR formulations, although a lower daily dose is taken compared with the ER formulations applied in this study. Trospium is metabolized by ester hydrolysis which may limit potential metabolic drug-drug interactions that may be observed after administration of antimuscarinics metabolized by the cytochrome p450 system.[31] Furthermore, as the parent compound may be largely eliminated unchanged in the urine, it is hypothesized that this medication may provide some local effects on the urothelium.[32]

The clinical effects of trospium chloride 20 twice daily was initially reported in a meta-analysis of two European placebo-controlled, double-blind, multicenter trials (RCTs).[33] In 517 patients randomized to placebo or trospium, trospium produced significant improvements in maximum cystometric bladder capacity (MCC), and urinary volume at first unstable detrusor contraction. The patients' subjective assessment of efficacy likewise significantly favored the trospium group. Similar frequencies of AEs were reported for trospium (35.7%) and placebo (38.9%).

Trospium IR was originally approved by the U.S. FDA in 2004 and the initial outcomes of this drug were documented in two U.S., 12-week, placebo-controlled RCTs.[34,35] In both trials, trospium IR twice daily significantly decreased the average number of daily voids, average urgency severity, urge frequency, and UUI episodes, while increasing the average volume per void. All improvements occurred by the end of the first week and all were sustained throughout the 12-week study.

Several studies have compared the clinical effects of trospium to oxybutynin. Amulticenter trial from the Czech Republic enrolled and randomized 358 patients to trospium 20 mg twice daily or oxybutynin 5 mg twice daily.[36] At intervals of up to 52 weeks, both drugs were associated with a significant reduction in micturition frequency and urgency episodes, and an increase in the MCC. Trospium was associated with a better benefit to risk ratio based on the higher incidence of anticholinergic AEs seen with oxybutynin. A second study from Germany aimed to demonstrate the efficacy and noninferiority of trospium IR to oxybutynin IR in treating UUI.[37] This active-controlled, parallel-group, multicenter, Phase IIIb RCT randomized 1658 patients to trospium 15 mg thrice-daily (TID) or oxybutynin 2.5 mg TID for 12 weeks. Daily doses could be adjusted upward after 4 weeks, to 90 mg of trospium (30 mg TID) and 15 mg of oxybutynin (5 mg TID), respectively, if needed. After 4 weeks, daily doses were doubled in 29.2% of patients in the trospium group and in 23.3% of patients in the oxybutynin group. Trospium was noninferior to oxybutynin in the reduction in the number of weekly UUI episodes after 4 and 12 weeks of treatment. In the full analysis set, the median change was −10.42 with trospium and −10.00 with oxybutynin ($P < 0.001$ for the noninferiority hypothesis). There was also no difference between groups regarding the observed reductions of daily micturitions and intensity of urgency as well as the increase in micturition volume at the end of 12 weeks. Visual analog scale (VAS), King's Health Questionnaire (KHQ), and the 36-Item Medical Outcomes Study Short-Form General Health Survey (SF-36) scores were improved to a similar extent in both treatment groups at the end of treatment. Worsening of dry mouth was less common in the trospium group than in the oxybutynin group after 4 and 12 weeks (46.9% vs. 63.9% and 51.2% vs. 64.4%, respectively; both time points, $P < 0.001$ between groups). Treatment-emergent adverse events (TEAEs) were reported by 22.7% of the trospium group and 26.5% of the oxybutynin group, with dry mouth the most frequently occurring AE (4.1% of the trospium group, 7.7% of the oxybutynin group).

The flexible dosing of anticholinergic medications is commonly performed to reach a maximum therapeutic effect balanced by the impact of AEs. While this strategy is most commonly employed with oxybutynin,[38] a recent post hoc analysis of the trial by Zellner et al provided information regarding the efficacy of

flexible dosing of trospium IR.[39] Bödeker et al showed that dose escalation of either trospium or oxybutynin increased the reduction in UUI episodes in the population studied. At study end, there were no relevant differences between the "dose adjustment" subgroups and the respective "no dose adjustment" subgroups (trospium: $P = 0.249$; oxybutynin: $P = 0.349$). This indicates that the total number of UUI episodes was indeed more reduced in patients with dose escalation by the end of treatment than in patients treated with the starting dosage. After dose escalation, worsening of dry mouth was higher in both dose adjusted subgroups compared to the respective "no dose adjustment" subgroups ($P < 0.001$). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups ($P < 0.001$) and TEAEs were increased in the dose-adjusted subgroups. The analysis suggested that there were ~30% of OAB patients in the trospium subgroup who might benefit from higher doses of medication to achieve therapeutic success. The gains in efficacy, however, must be balanced against the increase in AEs.

Trospium chloride ER (60 mg once daily)

In 2007, trospium ER gained U.S. FDA approval. The new formulation releases trospium using a capsule that contains pellets that dissolve in a time- and pH-dependent manner, lowering the maximum observed C_{max} and delivering the drug to maintain therapeutic levels over a 24-hour period.[40] C_{max} may be lower in the ER formulation and may result in an improvement in the AE profile while maintaining the efficacy of the twice-daily IR preparation. The steady-state pharmacokinetics of both IR and ER trospium formulations were recently characterized in a multidose, randomized, open-label, 2-period, 2-arm crossover study in 24 male and female subjects.[41] The authors observed a lower mean AUC from 0 to 24 hours (17,360 vs. 28,590 pg-h/mL; ratio 61%; 90% CI 51%–72%) and lower C_{max} (1517 vs. 2502 pg/mL; 61%; 90% CI 49%–75%) for the ER formulation, compared to the IR formulation. Additionally, the median time to C_{max} is later (5.0 vs. 4.5 hours) and $T_{1/2}$ is longer (35.8 vs. 27.2 hours) for the ER formulation.

The efficacy of trospium ER has also been evaluated in two large multi-institutional RCTs that included a total of 1165 patients.[42,43] In both studies, trospium ER resulted in significant improvements in all primary (daily urinary frequency and UUI episodes) and key secondary (urgency severity, voided volume, and daily urgency voids) efficacy outcomes at weeks 1 through 12. As with previous studies, benefits over placebo were apparent within the first week of treatment. The relative efficacy and safety of trospium IR and ER formulations was also recently reviewed.[44] Trospium ER appears to be as effective as the IR formulation in improving the key outcome parameters associated with OAB, but with a lower rate of dry mouth, the most common side effect of these agents. In comparison to other antimuscarinic agents, trospium has comparable efficacy and safety and was associated with good patient persistence with treatment.

Analyses of pooled data from the two identically-designed phase III RCTs of trospium ER have yielded additional information regarding its efficacy and tolerability in distinct patient subpopulations. The following manuscripts represent post-hoc analyses of the pooled data from the aforementioned large phase III RCTs. The effects of baseline incontinence disease severity on the treatment outcome with trospium ER was evaluated in one study.[45] Complete continence, defined as no UUI episodes on a 3-day bladder diary collected at week 12 of treatment, was the efficacy parameter under investigation. Baseline UUI levels were inversely correlated with the week 12 percentage of patients continent (PPC) ($P < 0.0001$) and post-treatment PPCs were higher with trospium than with placebo at all degrees of severity. Complete continence was achieved in 75% of trospium recipients with 1.0 UUI episodes/day at baseline and 48% of those with >1.0–2.0 UUI episodes/day at baseline.

Chancellor et al evaluated the impact of obesity on treatment success with trospium ER.[46] After stratifying the primary and secondary endpoints of the 1,165 study subjects by World Health Organization (WHO) obesity levels I and II, the authors determined that obesity was associated with a more severe baseline OAB state ($P < 0.01$). Trospium ER was more effective than placebo at reducing the number of daily toilet voids and UUI episodes ($P < 0.0001$) and at improving the secondary endpoints (PPC and urgency severity, $P < 0.0001$) for WHO obesity levels I and II. Likewise, treatment with trospium ER was associated with a significant improvement in HRQoL as assessed by the KHQ and the OAB questionnaire (OAB-q) at baseline and again at 12 weeks.[47] Trospium ER

produced significantly greater improvements from baseline than placebo in seven of nine KHQ domains. At week 12, the improvement in mean OAB-q HRQoL total score (~52 at baseline) was significantly greater with trospium ER than with placebo (+25.8 vs. +20.7, $P = 0.0003$). Improvements from baseline were seen with trospium ER on all eight of the OAB-q symptom bother subscales.

Sand et al performed a subgroup analysis of pooled data for subjects aged ≥ 75 years from the two RCTs.[48] The patients continued to a 9-month open-label extension period during which all subjects received trospium ER. A total of 143 subjects who were aged ≥ 75 years (85 trospium ER, 58 placebo; mean age 79 years; 73% female) were evaluated. At week 12 of the double-blind period, trospium ER produced greater improvements from baseline than placebo in primary voiding diary parameters (changes from baseline in the mean number of daily toilet voids and UUI episodes), OAB Patient Global Assessment, and QoL. Efficacy and tolerability persisted among subjects receiving open-label trospium ER for up to one year. A subgroup analysis was also performed on data from the 176 male patients with OAB (trospium ER, 94; placebo, 82) who participated in one of the two studies.[49] A history of benign prostatic hyperplasia (BPH) was recorded for 29 trospium ER recipients (30.9%) and 23 placebo recipients (28.0%). A total of 19 patients (20.2%) receiving trospium ER and 15 (18.3%) receiving placebo experienced ≥ 1 TEAE considered at least possibly related to the study medication. Two trospium ER patients (2.1%) developed urinary retention; both were aged ≥ 75 years, and one had a history of BPH. Treatment with trospium ER compared with placebo resulted in significantly greater decreases from baseline in the mean number of daily toilet voids (−2.5 vs. −1.5; $P < 0.05$) and UUI episodes (−2.3 vs. −1.4; $P < 0.05$) in men at week 12.

Ginsberg et al examined the effects of trospium ER on diurnal and nocturnal OAB symptoms.[50] Diurnal events were those occurring from arising from bed in the morning until retiring in the evening, while nocturnal events were those occurring from retiring until arising. At Week 12 comparison of trospium ER versus placebo, a significantly greater mean reduction from baseline in nocturnal voids (−0.8 vs. −0.6; $P = 0.006$) and diurnal voids (−1.9 vs. −1.4; $P < 0.0001$) was noted. At Week 12, the mean percent reduction from baseline with trospium ER versus placebo in nocturnal UUI episodes (−60.2% vs. −48.3%; $P = 0.003$) and mean absolute reduction in diurnal UUI episodes (−2.0 vs. −1.5; $P < 0.0001$) was significantly greater. Predictors of nocturnal response were duration (weeks) and type of therapy (trospium ER vs. placebo). Reductions in nocturnal toilet voids were accompanied by significant improvements in sleep-related QoL domains.

As OAB may be associated with various comorbidities and treatment of these may result in multiple medication use, Sand et al assessed the safety and efficacy outcomes with trospium ER in subjects with OAB who were taking multiple concomitant medications.[51] Predictors of TEAEs were identified by multivariate logistic regression analysis. Concomitant medications were being taken by 1135 subjects, and, among subjects taking seven or more concomitant medications (N = 427), there was no significant difference between trospium ER and placebo in the proportion of subjects experiencing one or more TEAEs (64.5% vs. 58.3%). Logistic regression analysis indicated that the odds of experiencing a TEAE were influenced by concomitant medication use, but not by randomization assignment to trospium or to placebo, suggesting that concomitant drugs contribute more to TEAEs than trospium ER. Compared with subjects taking one to two concomitant medications, the adjusted odds ratio (OR) for experiencing any TEAE was 3.39 (95% CI 2.39, 4.80; $P < 0.0001$) for subjects taking seven or more concomitant medications. The adjusted OR for experiencing any TEAE for subjects randomized to active treatment compared with placebo was 1.19 (95% CI 0.85, 1.67; $P = 0.31$). Efficacy in subjects taking seven or more concomitant medications was similar to that in the overall pooled study population.

Finally, results of the open label extension of the two trials have become available.[52] Following double-blind treatment, subjects with OAB could enter the open-label period, during which they received trospium ER once daily for 36 weeks. Of the 1,027 subjects who completed double-blind treatment, 944 (92%) continued into the open-label period (placebo-to-trospium, N = 483; trospium-to-trospium, N = 461); 332 (68.7%) and 335 (72.7%), respectively, completed the open-label period. At Week 48, the mean change from baseline in the number of daily toilet voids was −3.21 in

the placebo-to-trospium group and −3.35 in the trospium-to-trospium group, and the median change from baseline in the number of UUI episodes/day was −2.33 in both groups. Efficacy was maintained relative to Week 12 in trospium-to-trospium subjects, while improvement was seen following trospium initiation in placebo-to-trospium subjects. Improvement from baseline was also observed on secondary efficacy parameters at Week 48. As before, dry mouth and constipation were the most common TEAEs. Central nervous system AEs were rare and did not increase with long-term treatment.

Safety of trospium chloride

The safety of trospium IR was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients (1673 trospium, 1056 placebo, and 246 active control medications.[29] Of this total, 1181 patients participated in two, 12-week, Phase 3, U.S., efficacy and safety studies and a 9-month open label extension. In all placebo-controlled RCTs combined, the incidence of serious AEs was 2.9% among patients receiving trospium 20 mg twice daily and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possible related to treatment with trospium or placebo, respectively. TEAEs from the combined 12-week, U.S., trials for placebo and trospium, respectively, are: dry mouth (5.8% vs. 20.1%), constipation (4.6% vs. 9.6%), upper abdominal pain (1.2% vs. 1.5%), dyspepsia (0.3% vs. 1.2%), headache (2.0% vs. 4.2%), fatigue (1.4% vs. 1.9%), urinary retention (0.3% vs. 1.2%), and dry eyes (0.3% vs. 1.2%).

The safety of trospium ER was evaluated in two Phase 3 double-blind RCTs encompassing 1165 patients (578 trospium and 587 placebo).[53] There were 157 (27.2%) trospium ER patients and 98 (16.7%) placebo patients who experienced one or more TEAEs that were assessed by the investigator as at least possibly related to study medication. TEAEs from the combined trials for placebo and trospium, respectively, are: dry mouth (3.7% vs. 10.7%), constipation (1.5% vs. 8.5%), upper abdominal pain (0.3% vs. 1.4%), dyspepsia (0.7% vs. 1.2%), nausea (0.3% vs. 1.4%), urinary tract infection (0.9% vs. 1.2%), and dry eyes (0.2% vs. 1.6%).

As trospium is hydrophilic and positively-charged, it does not cross the blood-brain barrier (BBB). Several studies have provided additional information regarding trospium and its relationship to CNS AEs. Geyer et al investigated whether trospium may be a substrate of P-glycoprotein (P-gp), a transporter of many amphiphilic or positively charged drugs.[54] The authors confirmed the very low ability of trospium chloride to penetrate the BBB and demonstrated that, in mice, as an additional and biological protective barrier, the P-gp-mediated drug efflux at the BBB highly limits the brain penetration of this drug. The authors concluded that this mechanism is likely to be at least part of the reason for the reduced CNS side effects seen with trospium chloride.

In another trial, Staskin et al aimed to determine if trospium is assay-detectable in the CNS of older adults with OAB and to assess whether deterioration of memory occurs in these individuals.[55] Twelve cognitively intact older adults (≥65–75 years old) with OAB were given trospium ER over a 10-day period to achieve plasma steady-state levels. Standardized memory testing (Hopkins Verbal Learning Test-Revised and Brief Visuospatial Memory Test-Revised) was performed pre-dose (day 0) and post-dose (day 10). Trospium levels in all the cerebrospinal spinal fluid CSF samples of all participants were assay undetectable (<40 pg/ml) on day 10 at steady-state peak plasma concentration concurrent with measureable peak plasma values (C_{max} = 925 pg/ml). Repeat memory testing revealed no significant net drug effect on learning or recall.

Conclusions

Although trospium chloride has been used in Europe and Asia for over 20 years, it is a relatively novel addition to the antimuscarinic armamentarium for the pharmaceutical treatment of OAB in the U.S. Its quarternary amine structure minimizes CNS side effects owing to trospium's inability to cross the blood-brain barrier. Furthermore, as the parent compound is eliminated essentially unchanged in the urine, trospium may provide additional benefit due to a local effect on the urothelium. The immediate-release formulation has been shown to be effective compared to placebo and non-inferior to immediate-release oxybutynin. While flexible dosing has the potential to decrease the number of daily voids and UUI episodes, there is a concomitant increase in the occurrence of AEs such as dry mouth. Level I evidence is now available to support the efficacy of extended-release trospium chloride,

and, as expected, the rates of treatment-related dry mouth and constipation exceed those seen with placebo. CNS side effects are rare and memory and cognition do not appear to be impaired in the elderly treated with trospium ER. Several subanalyses of the pooled data from two large RCTs have demonstrated the efficacy of trospium ER in subpopulations such as men, the elderly, the obese, and those with nocturnal and diurnal symptoms. Finally, open label extensions have demonstrated continued efficacy and persistence with trospium therapy. While we await head-to-head crossover studies to provide definitive information regarding the comparative efficacy of different antimuscarinics, current evidence suggests that trospium chloride should be considered as a primary option for pharmaceutical treatment of OAB.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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