Obesity Is Associated With a More Severe Overactive Bladder Disease State That Is Effectively Treated With Once-Daily Administration of Trospium Chloride Extended Release

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Aims: Obesity is an established risk factor for urinary incontinence, yet no information exists as to the efficacy of antimuscarinic agents in this population. The goal of this study is to examine the efficacy of once daily trospium chloride (SancturaTM) XR in overweight and obese patients with the overactive bladder syndrome. Methods: The primary and secondary end-points of the 1,165 study subjects from the integrated trospium chloride XR pivotal trials were stratified by World Health Organization (WHO) obesity levels I and II. Results: Obesity (WHO level I, II criteria) was associated with a more severe baseline OAB disease state (P < 0.01). Trospium chloride XR was more effective than placebo at reducing the primary endpoints (toilet voids, UUI, P < 0.0001) and at improving the secondary end-points (percent patients continent and urgency severity, P < 0.0001) for WHO obesity levels I and II. Conclusions: Obesity is associated with a more severe OAB disease state. Once daily trospium chloride XR is efficacious in the obese patient with the OAB syndrome. Neurourol. Urodynam. 29:551–554, 2010. © 2010 Wiley-Liss, Inc.

Key words: incontinence; leakage; obesity; overactive bladder syndrome; trospium; urge incontinence; urgency

INTRODUCTION

Obesity is an increasing health problem world-wide, and several epidemiological studies have identified a positive association between obesity and an increased incidence of urinary incontinence.1–5 Specifically, a positive correlation between body mass index (BMI) and incontinence has been reported, and this association has been demonstrated for all subtypes of incontinence (stress, mixed, and urge), particularly severe combined urge urinary and stress incontinence.6 In women, but not in men, the prevalence of wet OAB has been shown to be positively related to increasing BMI.7,8 In the NOBLE study, wet OAB was 2.2 times more prevalent in women with a BMI of 30 or more than in those with a BMI under 24 kg/m2.9 In the Heart and Estrogen/Progestin Replacement study (HERS), increasing BMI was found to be a significant predictor of combined urge and stress incontinence.10 Thus, the epidemiological evidence supports an association between obesity, the OAB syndrome and incontinence.

Although behavioral modifications and weight loss have been associated with improved continence,5,11,12 no prior reports exist regarding the efficacy of antimuscarinic pharmacotherapeutics in obese patients with the OAB syndrome. The objective of this study was to evaluate the efficacy of trospium chloride once daily 60 mg XR for reducing urgency, urinary frequency, and urgency urinary incontinence in obese patients stratified according to the BMI.

METHODS

Patients

This post hoc analysis is based on integrated data from two multicenter, randomized, double-blind, placebo-controlled phase III trials that have been separately reported.13,14 Patient inclusion criteria were male or female patients aged ≥18 years with OAB for ≥6 months. Patients were required to have urgency frequency (an average of ≥10 toilet voids per day), symptoms of urgency (at least 1 “severe” urgency severity rating associated with a toilet void per 3 days, as measured by the Indevus Urgency Severity Scale [IUSS]);15 and an average of ≥1 urge urinary incontinence (UUI) episode per day, as recorded in a baseline 3-day patient urinary diary. Patients were excluded if they had a total void volume of >3,000 mL per day, stress incontinence, insensate continence; history of neurogenic bladder; significant renal disease; urinary tract infections; and bladder obstructions. BMI was not an inclusion or exclusion criteria. Patients currently receiving drug treatment for OAB were allowed to enter the study following a 7-day washout period prior to the urinary diary collection.

Study Design and Procedure

Patients were randomized on a 1:1 basis to receive placebo or trospium chloride 60 mg XR once daily for 12 weeks. Randomization was stratified according to the mean number of toilet voids per day at baseline. The primary study endpoints were: 24-hr toilet voids and urgency urinary incontinence (UUI). The secondary endpoints were: percent patients continent (PPC), urgency severity, volume voided, and

Conflicts of interest: Dr. Oefelein—Director: Allergan, Dr. Chancellor—Consultant, Speaker honorarium, trial participant: Allergan.

Dirk De Ridder led the review process.

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complete response rate. For the post hoc analysis, patients were stratified according to the World Health Organization (WHO) obesity criteria using baseline BMI values: WHO level I: BMI ≥ 30 kg/m² versus < 30 kg/m² and WHO criteria level II: BMI ≥ 35 kg/m² versus BMI < 35 kg/m². BMI is a useful index in estimating obesity.

Efficacy Outcomes

The primary end-points for both phase III studies were the change from baseline in mean number of toilet voids and UUI episodes per day, collected from 3-day patient diaries at weeks 1, 4, and 12. The secondary end-points reported herein include: PPC, and urgency severity at weeks 1, 4, and 12. Safety was assessed via adverse event monitoring, electrocardiograms, physical examination, clinical laboratory tests, and vital signs.

Statistical Analysis

A rank ANOVA model with week, treatment, polypharmacy (i.e., multiple concomitant medication use) and all second and third degree interactions (for sliced tests) as fixed effects was used for all continuous data. Logistic regression with week, treatment, polypharmacy (use of multiple concomitant medications) and all second and third degree interactions (for sliced tests) as fixed effects was used for categorical data. A multivariate analysis to predict any post-dose adverse events was also performed. The model included demographic parameters (race, gender, age, height, weight, BMI, BSA—body surface area, IBW—ideal body weight), randomized treatment (placebo vs. trospium XR), multiple medication use, and baseline efficacy parameters (toilet voids, UUI, volume voided, and urgency severity).

RESULTS

A total of 1,165 patients were enrolled into the two studies and randomized to receive placebo (n = 578) or trospium 60 mg XR (n = 578). Of these, 1,129 patients had a calculable BMI and were stratified into WHO level I: BMI ≥ 30 kg/m² (n = 598) versus BMI < 30 kg/m² (n = 531) and WHO criteria level II: BMI ≥ 35 kg/m² (n = 335) versus BMI < 35 kg/m² (n = 794). The mean age and BMI for the study group were 60 years (range 21–90) and 32 kg/m² (range 16–67), respectively.

Toilet Voids and Urgency Urinary Incontinence

At baseline, the mean number of daily toilet voids was significantly (P < 0.01) greater among study subjects who had higher BMI values compared to those with lower BMI values (Table I). At week 12, trospium XR produced significantly greater mean reductions and mean percent reductions from baseline in the average daily number of toilet voids in both the higher and lower BMI subgroups (Fig. 1). Statistically significant (P < 0.05) differences between trospium XR and placebo were seen from week 1 onwards. Study subjects in the WHO level I or II obesity groups had significantly (P < 0.01) more UUI episodes at baseline compared with the corresponding less obese subjects (Table I). At week 12, trospium XR produced significantly (P < 0.001) greater median reductions and median percent reductions from baseline in the average daily number of UUI episodes in both WHO obesity classification (Fig. 2). Statistically significant (P < 0.05) differences between trospium XR and placebo were seen from week 1 onwards.

TABLE I. Average Number of Toilet Voids, Urge Urinary Incontinence (UUI) Episodes Per Day and Urgency Severity Score at Baseline, According to Both the WHO Obesity Levels I and II Stratification

<table>
<thead>
<tr>
<th></th>
<th>Toilet voids</th>
<th>UUI episodes</th>
<th>Urgency severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO level I</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMI &lt; 30 kg/m²</td>
<td>12.5</td>
<td>3.6</td>
<td>1.8</td>
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<td>BMI ≥ 30 kg/m²</td>
<td>13.1</td>
<td>4.5</td>
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<td>P-value</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td>WHO level II</td>
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<td></td>
<td></td>
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<tr>
<td>BMI &lt; 35 kg/m²</td>
<td>12.7</td>
<td>3.8</td>
<td>1.9</td>
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<tr>
<td>BMI ≥ 35 kg/m²</td>
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<td>4.7</td>
<td>2.0</td>
</tr>
<tr>
<td>P-value</td>
<td>0.01</td>
<td>&lt;0.01</td>
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Thus, while the higher BMI study subject subgroup had more severe baseline OAB symptoms, trospium chloride XR effectively reduced symptoms in those study subjects as well as in the corresponding lower-BMI subgroup. Notably, the efficacy observed in each BMI subgroup was consistent with that observed in the overall study population.

**Percent Patients Continent**

At baseline, all study subjects were incontinent and the PPC was zero. At the 12-week study end-point, the PPC on all 3 days of a 3-day diary stratified by WHO levels I and II are summarized in Figure 3. For all obesity states, trospium chloride XR was statistically superior to placebo, and this effect was observed as early as week 1.

**Urgency Severity**

At baseline, the average urgency severity associated with toilet voids was significantly ($P \leq 0.01$) greater in the higher versus the lower BMI subjects according to the WHO levels I and II obesity stratification (Table I). The mean % reduction in urgency severity associated with toilet voids is significantly reduced in the trospium XR treatment arm over placebo at all weeks (1, 4, and 12) and by all obesity states. At week 12, trospium XR produced significantly ($P \leq 0.001$) greater mean reductions and mean percent reductions from baseline in urgency severity associated with toilet voids in all obesity subgroups (Fig. 4). Furthermore, the drug to placebo ratios were particularly robust in the more obese patient population. Statistically significant ($P < 0.01$) differences between trospium XR and placebo were seen from week 1 onwards.

**Adverse Events**

A multivariate analysis to predict any post-dose adverse events was also performed. The model included demographic parameters (race, gender, age, height, weight, BMI, BSA, IBW), randomized treatment (placebo vs. trospium XR), multiple medication use, and baseline efficacy parameters (toilet voids, UIUI, volume voided, and urgency severity). In this multivariate model, neither BMI nor IBW were associated with an increased risk of AEs.

**DISCUSSION**

This analysis of the integrated data from two multicenter, randomized, double-blind, placebo-controlled clinical trials demonstrate that obese OAB study subjects have greater baseline symptom severity, and that trospium chloride XR significantly reduces OAB symptoms despite the greater disease severity associated with larger BMI. In particular, trospium XR increased the PPC and reduced the total number of toilet voids, urge urinary incontinence episodes and urgency severity across all BMI sub-groups. These improvements were significant and apparent within the first week of treatment.

Obesity and overweight are established risk factors for OAB in women, but the association is less clear in men. The exact mechanisms linking obesity and OAB are largely unknown. It has been hypothesized that excess body weight increases intra-abdominal pressure which in turn increases bladder pressure and intravesical pressure. The ongoing Program to Reduce Incontinence by Diet and Exercise (PRIDE) study has reported results that support the association of BMI and abdominal circumference with intra-abdominal and intravesical pressure. Further neurophysiologic and urodynamic studies are needed to fully investigate the association between obesity and OAB.

One possible mechanism of action orchestrating the interaction between obesity and OAB involves ghrelin—a peptide hormone linked to obesity and metabolism. Ghrelin has been reported to relax smooth muscle tone in the eye, uterus and heart. Tyagi et al. demonstrated the expression of mRNA for the ghrelin receptor—growth hormone secretagogue receptor (GSHR)—in human bladder. Furthermore, Tyagi and coworkers identified physiologic differential effects in rat bladder strips. The ghrelin relaxant effect was more pronounced in strips taken from lean (low body weight) rats than from obese rats. From these studies, it is hypothesized that the low plasma ghrelin levels observed in obese OAB patients, may up-regulate the expression of GSHR in the bladder, which may diminish detrusor storage function. Future studies are warranted to determine if there is a new biological basis for obesity link with the overactive bladder.
Weight loss has been reported to reduce urinary incontinence, and has been endorsed as an important treatment component. Although weight reduction effectively improves urinary incontinence, weight loss is notoriously difficult to maintain long-term. In addition, the benefit of weight loss with regard to UUI is less clear than that for stress incontinence. Thus, there remains a role for pharmacotherapeutic agents that are effective in the treatment of OAB irrespective of patient BMI.

The pharmacokinetic properties of antimuscarinic agents, such as hydrophilicity, metabolism and renal versus hepatic elimination may be clinically relevant in the treatment of OAB patient subsets and specifically obese patients with the OAB syndrome. A large percentage (60%) of metabolically active trospium chloride is eliminated through renal tubular secretion. The renal clearance of the hydrophilic trospium chloride molecule is also increased as BSA increases. Pre-clinical and clinical data support a local urothelial mechanism of action for trospium. These pharmacokinetic and molecular properties may ultimately establish an important role for trospium in obese patient with the overactive bladder syndrome.

Study Limitations

The primary study limitation is that this is a post hoc analysis of outcomes stratified by WHO levels I and II obesity states. The demographics of the enrolled patients in the phase III trials indicate a high proportion of patients were obese (mean BMI = 32 kg/m²). Obesity was not an inclusion or exclusion enrollment criteria. Therefore, the BMI of these study subjects likely reflects the overall association of obesity with the OAB syndrome and not a selection effect. It is important to note that the WHO criteria are externally establishing standards, which reduce the concern for arbitrarily defining obesity to influence the study outcomes. Although the baseline OAB disease severity (as measured by toilet voids, UUI, and urgency severity) was statistically more severe in the more obese study population (Table I), the clinical significance of this observation is unknown.

CONCLUSION

In conclusion, obese patients with the OAB syndrome have a more severe baseline disease state. Trospium chloride XR is effective in obese patients with the overactive bladder syndrome. Efficacy (UUI, toilet voids, PPC, and urgency severity) over placebo was observed as early as week 1 post-dose. Lastly, adverse events associated with trospium chloride XR were not more likely in obese versus non-obese OAB patients.

REFERENCES