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Efficacy and Safety of Flexible Dose Fesoterodine in Men and Women with Overactive Bladder Symptoms Including Nocturnal Urinary Urgency

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Abstract

Purpose—Awakening from sleep to urinate is the hallmark of nocturia, a condition that impacts several facets of health related quality of life and for which current therapy is suboptimal. Given the paucity of prospective data on antimuscarinics for the management of nocturia, we investigated the efficacy and safety of flexible dose fesoterodine for the treatment of nocturnal urgency in subjects with nocturia and overactive bladder.

Materials and Methods—Subjects with 2 to 8 nocturnal urgency episodes per 24 hours began a 2-week, single-blind, placebo run-in followed by 1:1 randomization to 12 weeks of double-blind treatment with fesoterodine (4 mg daily for 4 weeks with an optional increase to 8 mg) or placebo using predefined criteria for nocturnal urgency episodes, nocturnal urine volume voided and total 24-hour urine volume voided. The primary end point was change from baseline to week 12 in the mean number of micturition related nocturnal urgency episodes per 24 hours.

Results—Overall 963 subjects were randomized from 2,990 screened, and 82% of subjects treated with fesoterodine and 84% of those treated with placebo completed the study. Significant improvements in the primary end point (−1.28 vs −1.07), in nocturnal micturitions per 24 hours (−1.02 vs −0.85) and in nocturnal frequency urgency sum (−4.01 vs −3.42) were observed with fesoterodine vs placebo (all $p < 0.01$). Health related quality of life measures (overactive bladder questionnaire Symptom Bother −20.1 vs −16.5, sleep 22.3 vs 19.9 and other domains; all $p < 0.05$) were improved with fesoterodine.

Conclusions—To our knowledge this is the first prospective study to assess antimuscarinic efficacy for reducing nocturnal urgency. Flexible dose fesoterodine significantly reduced nocturnal urgency episodes vs placebo in subjects with overactive bladder.

Keywords

muscarinic antagonists; urinary bladder; overactive; nocturia; lower urinary tract symptoms; treatment outcome

Nocturia, waking from sleep at night to void, is highly prevalent in the general medical population and is increasingly recognized as important.^{1,2} Data indicate a strong association of nocturia with impaired HRQL, increased economic burden due to reduced work productivity, morbidity related to accidental falls and fractures, and increased mortality.^{1–6} Nocturia is the most common symptom leading to sleep disruption across a wide spectrum of ages.^{1–6} Current therapy for nocturia is unsatisfactory, in part due to the existence of multiple underlying causes.⁷

Nocturia is a symptom of overactive bladder syndrome, the hallmark of which is urinary urgency.⁸ Patients with nocturnal urgency may be particularly at risk for complications, including nighttime falls and fractures likely related to the need to rush to the bathroom to avoid incontinence.^{9,10} Currently recommended interventions for OAB are well established¹¹ but the optimal treatment of nocturnal urgency remains undefined.

Fesoterodine is an antimuscarinic agent approved for the treatment of OAB. To date there are no prospective studies that assess antimuscarinics in the treatment of nocturnal urgency as a primary outcome. Based on this uncertainty in the literature, we tested the hypothesis that fesoterodine would be superior to placebo in the treatment of nocturnal urgency in patients with OAB with nocturia.

MATERIALS AND METHODS

This was a 12-week, randomized, double-blind, placebo controlled trial conducted between August 2009 and September 2011 at 108 sites throughout the United States (ClinicalTrials.gov ID NCT00911937). The study protocol was approved by the appropriate institutional review boards and independent ethics committees, and subjects provided written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guideline on Good Clinical Practice.

Adults age 18 years or older with self-reported OAB symptoms, including nocturnal urgency for 3 or more months before screening, and a mean of 8 or more micturitions per 24 hours, 3 or more urgency episodes per 24 hours, and 2 to 8 nocturnal urgency episodes per 24 hours on bladder diary at screening were eligible. Urgency episodes were defined as those rated 3 or more on the Urinary Sensation Scale.¹² Nocturnal urgency episodes were defined as those rated 3 or more on the USS and recorded in the bedtime section of the diary (ie the time between when the subject intended to go to sleep and the time the subject arose the next day). Key exclusion criteria were any condition contraindicating fesoterodine use; clinically significant hepatic or renal disease; treatment with potent CYP3A4 inhibitors; intermittent or unstable use of tricyclic antidepressants, estrogens, diuretics, alpha-blockers or 5-alpha reductase inhibitors; pregnancy or nursing; recent history/known diagnosis of any sleep disorder; nocturia due to uncontrolled conditions other than OAB including chronic heart failure, diabetes mellitus, diabetes insipidus or polyuria (ie 24-hour urine volume greater than 3,500 ml); history of acute urinary retention requiring catheterization or severe voiding difficulties in opinion of the investigator; use of indwelling catheter or intermittent self-catheterization; predominant stress urinary incontinence; urinary tract infection based on results of urinalysis at screening or recurrent urinary tract infections (ie treatment for urinary tract infection more than 3 times in the last year); initiation of electrostimulation, formal bladder training or pelvic floor exercises within 4 weeks of screening; prior use of study medication; or treatment with antimuscarinic OAB medication within 2 weeks of screening.

After a 2-week screening, subjects with 2 to 8 nocturnal urgency episodes per 24 hours who met other study entry criteria began a 2-week, single-blind, placebo run-in period. After the

run-in, subjects with a 35% or less decrease in nocturnal urgency episodes per 24 hours from screening to baseline, 2 to 8 nocturnal urgency episodes per 24 hours on baseline diary, total urine volume 3,500 ml or less recorded on 1 of 3 baseline diary days, and nocturnal urine volume voided of 50% or less of total 24-hour urine volume voided recorded on 1 of 3 baseline diary days were eligible for randomization.

Eligible subjects were randomized in double-blind fashion to 4 mg fesoterodine or matching placebo (1:1 ratio) once daily for the first 4 weeks via a centralized randomization system (Impala). The randomization schedule was generated, secured, distributed and stored by the sponsor. At week 4, based on subject-investigator discussions regarding efficacy and tolerability, the investigator could increase the fesoterodine dose to 8 mg once daily or continue the subject on the 4 mg dose for the remaining 8 weeks of the study (sham dose escalation or maintenance for placebo). No further dose adjustments were permitted after week 4. Study medication was to be taken once daily within 4 hours of bedtime.

Subjects completed a 3-day bladder diary at screening (week 4), the beginning of the placebo run-in (week 2), the end of the placebo run-in (baseline, week 0), week 4 and week 12, in which they recorded the time of each micturition and whether it occurred during awake time or bedtime. Subjects rated the urgency sensation associated with each recorded micturition using the 5-point USS (1—no feeling of urgency, 2—mild feeling of urgency, 3—moderate feeling of urgency, 4—severe feeling of urgency, 5—unable to hold urine).¹² Subjects recorded the volume of urine voided for each micturition for 1 of the 3 days in diaries completed at baseline and week 12. The primary end point was the change from baseline to week 12 in mean number of micturition related nocturnal urgency episodes per 24 hours. Secondary diary end points included change from baseline to week 12 in nocturnal micturitions, nocturnal frequency-urgency sum (sum of USS ratings recorded for all nocturnal micturitions), mean voided volume per nocturnal micturition, total micturitions, urgency episodes, urgency urinary incontinence episodes, frequency-urgency sum (sum of USS ratings recorded for all micturitions) and mean voided volume per 24 hours.

Subjects completed the OAB-q at baseline and week 12.¹³ The OAB-q comprises an 8-item Symptom Bother scale and a 25-item HRQL scale with 4 domains (concern, coping, sleep and social interaction). Scores on each scale and domain are normalized to 0 to 100.¹³ Higher scores on the Symptom Bother scale reflect greater bother. Higher scores on the HRQL scale and domains reflect better HRQL. The minimally important difference (ie the smallest change from baseline that is clinically meaningful) is 10 points for each OAB-q scale and domain.¹⁴ Subjects completed the modified Berlin questionnaire at the start of the placebo run-in to estimate the probability of obstructive sleep apnea.^{15,16} As an exploratory end point, subjects completed the ESS to quantify subjective sleepiness at baseline, week 4 and week 12.¹⁷

Based on previous studies, the estimated sample size was 426 subjects per group to provide approximately 80% power to detect a clinically meaningful difference of 0.25 or more episodes per 24 hours in mean change from baseline to week 12 in nocturnal urgency episodes (assuming SD 1.3) between fesoterodine and placebo using a 2-sided t test with an alpha of 5%. Allowing for a dropout rate of 8%, 928 randomized subjects (464 per group) were required. A blinded sample size re-estimation conducted when 341 subjects completed the study, indicating that no increase in sample size was necessary.

Diary, OAB-q and ESS data analyses were based on the full analysis set (ie all subjects who took 1 dose or more of study drug, and had at least a baseline and a post-baseline efficacy assessment). The differences between the fesoterodine group and the placebo group in mean change from baseline to week 12 for each end point was assessed using an ANCOVA

model, with terms for treatment and center and baseline value as a covariate. Baseline covariates were modeled as strictly linear. Statistical analyses were performed using SAS® software. Missing data were imputed using the last observation carried forward method. Statistical tests of efficacy were 2-sided with a significance level of 0.05. Adverse events were monitored throughout the study and assessed descriptively using the safety analysis set (ie all subjects who were randomized and took 1 dose or more of the study drug).

RESULTS

Of the 2,990 subjects screened 963 (32%) were randomized to treatment with fesoterodine or placebo. Overall 381 of 476 subjects (82%) treated with fesoterodine and 400 of 487 subjects (84%) given placebo completed the study (fig. 1). The full analysis and safety analysis sets for the placebo group included 474 subjects, and the full analysis and safety analysis sets for the fesoterodine group included 463 subjects. Subject characteristics were comparable between groups (supplementary table 1, <http://jurology.com>). Overall 61% (282 of 463) of subjects in the fesoterodine group and 67% (317 of 474) of those in the placebo group were escalated to 8 mg or matching placebo, respectively, at week 4.

Change from baseline in mean number of micturition related nocturnal urgency episodes per 24 hours at week 12 (primary end point) was significantly greater with fesoterodine than placebo (-1.28 vs -1.07 , $p = 0.003$; supplementary table 2, <http://jurology.com>). The decrease in the number of nocturnal micturitions per 24 hours was significantly greater with fesoterodine vs placebo ($p = 0.011$). The nocturnal frequency-urgency sum, which reflects the number of micturitions and urgency sensation, was similarly improved ($p < 0.003$). Improvements in mean voided volume per nocturnal void were not statistically significantly different between the fesoterodine and placebo groups ($p = 0.855$). Improvements in total micturitions ($p = 0.001$), urgency episodes ($p < 0.001$) and frequency-urgency sum ($p < 0.001$) per 24 hours were significantly greater with fesoterodine vs placebo. Improvements in urgency urinary incontinence episodes per 24 hours ($p = 0.217$) and mean voided volume per micturition per 24 hours ($p = 0.840$) were not significantly different between fesoterodine and placebo.

Improvements on the OAB-q Symptom Bother scale ($p < 0.001$); total HRQL scale ($p = 0.010$); and the sleep ($p = 0.022$), concern ($p = 0.011$), coping ($p = 0.020$) and social interaction ($p = 0.046$) domains were significantly greater with fesoterodine than with placebo (fig. 2). Change from baseline to week 12 on the ESS was not significantly greater with fesoterodine vs placebo (-2.3 ± 0.2 vs -1.9 ± 0.2 , 95% CI for treatment difference -0.8 to 0.11 , $p = 0.131$).

Of 937 subjects in the safety analysis set 188 (41%) in the fesoterodine group and 152 (32%) in the placebo group reported treatment emergent adverse events. Most of these were mild or moderate in intensity. The most common adverse events were dry mouth, constipation and headache (see table). Twenty-five subjects (5%) in the fesoterodine group and 10 (2%) in the placebo group withdrew from the study because of adverse events. Serious adverse events occurred in 5 (1.1%) subjects in the fesoterodine group and 9 (1.9%) subjects in the placebo group, including 1 death in the placebo group. None of the serious adverse events was considered treatment related in the opinion of the investigator. Investigator defined urinary retention and patient reported dysuria were reported by 3 (0.6%) and 2 (0.4%) subjects in the fesoterodine group, and 1 (0.2%) and 1 (0.2%) subject in the placebo group, respectively. Only 1 subject with urinary retention required catheterization (placebo group).

DISCUSSION

Our results contribute to the literature in several important ways. We demonstrated that fesoterodine is superior to placebo in reducing nocturnal urgency episodes (primary outcome). We also observed improvements in clinically important secondary outcomes including nocturia, multiple domains of HRQL, urinary frequency and urgency. We observed few clinically important side effects associated with fesoterodine in this demographically broad study population. To our knowledge, fesoterodine is the first antimuscarinic agent to show significant efficacy in a trial designed to assess improvement in nocturnal urgency.

Other agents are available for the treatment of nocturia, including timed diuretics,⁹ alpha-blockers,¹⁰ vasopressin agonists,^{10,18} behavioral treatments^{9,10} and combination therapies.^{7,19,20} However, at present there are no medications approved by the Food and Drug Administration for the treatment of nocturia. In addition, our primary outcome of nocturnal urgency has not been the focus of any prior prospective randomized trials.

Considerable data are available regarding the efficacy of various antimuscarinic agents on nocturia. The results are mixed, with some studies showing benefit and others not, and many have been based on secondary or pooled analyses rather than a primary focus. Prior secondary analyses have assessed the role of extended release tolterodine for the treatment of nocturnal urgency in a population of patients with OAB reporting nocturia.^{21,22} In this cohort nocturia was not significantly improved with tolterodine. However, post hoc analyses from this prior study showed improvements in nocturnal urgency.²² These exploratory results are subject to the limitations of post hoc analyses (eg the authors did not recruit patients with major symptoms of nocturnal urgency) and have not been reproduced to date. Brubaker and FitzGerald performed a pooled analysis²³ from 4 prior trials^{24,25} to assess the effect of solifenacin on nocturia. The authors focused on patients with OAB, assessing the impact of nocturnal polyuria on outcomes. They did observe some improvements in patients without nocturnal polyuria, although the magnitude of the placebo response in the nocturnal polyuria group was considerable and may have driven some of the findings. Subgroup analyses focusing on nocturia showed some improvement in nighttime micturitions and sleep related variables in subjects treated with solifenacin.²⁶ Trospium chloride has been shown to decrease nocturnal frequency.^{27,28} However, whether these agents improve nocturnal urgency remains unclear.

Strengths of our study include a large sample size with strictly predefined primary outcome measures focusing on a clinically relevant problem. However, we acknowledge a number of limitations. We did not measure polysomnograms to exclude sleep apnea and other sleep disorders associated with nocturia. We made this decision because this testing can be cumbersome and is not the current standard of care for the evaluation and treatment of these patients, particularly in urology clinics. Scores on the modified Berlin questionnaire, administered at baseline, suggested that the probability of obstructive sleep apnea was low in the majority of subjects. However, it is possible, if not likely, that some patients with undiagnosed sleep disorders were included in our sample, which may have influenced our results. Further research will be required to determine the optimal treatment for individuals with sleep disorders and nocturnal urgency.

One could also question the magnitude of our observed effect size, despite our significant primary outcome. We view the improvement seen with fesoterodine as robust and clinically important. However, we recognize that there is no established minimal important difference to identify a meaningful change in nocturnal urgency. Furthermore, we acknowledge that some of the benefit seen with fesoterodine may have been due to a placebo effect, which in

OAB trials may be related to close monitoring and self-tracking of bladder symptoms. Indeed, some data suggest that keeping simple diaries may have a positive impact on lower urinary tract symptoms.²⁹ In anticipation of improvements in the control arm as seen in prior studies in this field, we did perform a placebo run-in to exclude patients with an exaggerated response to placebo. In this trial fesoterodine produced a mean reduction of 1.28 nocturnal urgency episodes per night, which was statistically superior to placebo and which we considered to be clinically significant. Finally, to maximize generalizability we did not control variables such as fluid intake and the investigators were allowed to use their clinical impressions regarding dose escalation. We did not require investigators to use specialized technology such as urodynamic studies, uroflowmetry or bladder ultrasound to guide therapy. Despite these limitations, we believe that our findings are robust and add to the literature in a clinically important manner as the information may impact patient care.

CONCLUSIONS

We observed the benefits of fesoterodine on our primary outcome of nocturnal urgency in a population with OAB in a carefully designed study. We encourage further research on assessment of how improved nocturnal urgency impacts the risk of falls and sleep architecture, including associated cardiometabolic and mortality outcomes.

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Abbreviations and Acronyms

ESS	Epworth Sleepiness Scale
HRQL	health related quality of life
OAB	overactive bladder syndrome
OAB-q	overactive bladder questionnaire
USS	Urinary Sensation Scale

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Figure 1.
Subject disposition

Figure 2.

Change from baseline to week 12 in OAB-q scores. Higher scores on HRQL scale and 4 domains indicate improvement (decreased impact of OAB on patient lives). Lower scores on Symptom Bother scale indicate improvement (decreased bother).

Table

Summary of adverse events

	No. Placebo (%)	No. Fesoterodine (%)
All adverse events	152 (32.1)	188 (40.6)
Serious adverse events *	9 (1.9)	5 (1.1)
Adverse events occurring in 2% or more of subjects:		
Dry mouth	36 (7.6)	98 (21.2)
Constipation	7 (1.5)	15 (3.2)
Headache	5 (1.1)	11 (2.4)
Discontinuations due to adverse events:	11 (2.3)	25 (5.4)
Dry mouth	0	4 (1.9)
Constipation	2 (0.4)	1 (0.2)
Urinary retention	1 (0.2)	3 (0.6)

* None of the serious adverse events in either group was considered treatment related.