Effect of Fesoterodine in Vulnerable Elderly Subjects with Urgency Incontinence: A Double-Blind, Placebo Controlled Trial

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Purpose: We evaluated the efficacy and safety of flexible dose fesoterodine in medically complex vulnerable elderly subjects with urgency urinary incontinence.

Materials and Methods: In this 12-week, randomized, double-blind, flexible dose, placebo controlled trial, subjects were community dwelling men and women 65 years old or older. Subjects had scores of 3 or more on the VES-13 (Vulnerable Elders Survey) and 20 or more on the MMSE (Mini-Mental State Examination), and 2 to 15 urgency urinary incontinence episodes and 8 or more micturitions per 24 hours on 3-day baseline diaries. Subjects randomized to fesoterodine received 4 mg once daily for 4 weeks and could then increase to 8 mg based on discussion with the investigator. Subjects receiving 8 mg could decrease the dose to 4 mg at any time (sham escalation and de-escalation for placebo). The primary outcome measure was change in daily urgency urinary incontinence episodes. Secondary outcomes included changes in other diary variables and patient reported quality of life measures. Safety evaluations included self-reported symptoms and post-void residual volume.

Results: A total of 562 patients were randomized (mean age 75 years, 50.4% age 75 years or greater). Subjects had high rates of comorbidities, polypharmacy and functional impairment. At week 12 the fesoterodine group had significantly greater improvements in urgency urinary incontinence episodes per 24 hours

Abbreviations and Acronyms

AEs = adverse events

HRQL = health related quality of life

OAB = overactive bladder

PVR = post-void residual urinary volume

UUI = urgency urinary incontinence

VE = vulnerable elderly

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Study received institutional review board approval.

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Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 564 and 565.

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(−2.84 vs −2.20, p = 0.002) and most other diary variables and quality of life, as well as a higher diary dry rate (50.8% vs 36.0%, p = 0.002). Adverse effects were generally similar to those of younger populations including risk of urinary retention.

Conclusions: To our knowledge this is the first antimuscarinic study in a community based, significantly older, medically complex elderly population with urgency urinary incontinence. Flexible dose fesoterodine significantly improved urgency urinary incontinence episodes and other outcomes vs placebo, and was generally well tolerated.

Key Words: muscarinic antagonists; urinary bladder, overactive; fesoterodine; urinary incontinence, urge; vulnerable populations

URGENCY urinary incontinence severely impacts the health of many older adults. UUI is associated with many comorbidities including falls and fractures, skin breakdown, depression and functional impairment.[1] In older individuals UUI is associated with an increased risk of institutionalization.[1] The prevalence, severity and cost of UUI increase with age,[1] with much of the cost attributable to absorbent products and nursing home care.

Despite the burden and cost of UUI in older persons, little is known regarding the efficacy and safety of antimuscarinic treatment in this population. Most available data come from post hoc subanalyses of trials with relatively small proportions of subjects older than 65 years, and especially older than 75 years.[2–8] There are few published prospective studies of antimuscarinics in healthy older patients,[9–11] and no studies have assessed the efficacy, safety and tolerability of antimuscarinics for the treatment of UUI in medically complex VE individuals. Such patients experience the greatest disease burden and potentially have the most to gain from treatment, but may be most at risk for adverse effects. Prospective trials in frail older adults only examined oxybutynin.[12–17] These trials had methodological flaws and/or failed to achieve efficacy. Therefore, we evaluated the efficacy and safety of flexible dose fesoterodine vs placebo in VE subjects with urgency urinary incontinence.

METHODS

This randomized, double-blind, placebo controlled, parallel group, multicenter trial was conducted at 108 United States sites between September 2009 and May 2011 (ClinicalTrials.gov Identifier: NCT00928070) in accordance with the Declaration of Helsinki[18] and the ICH (International Conference on Harmonisation) guideline on Good Clinical Practice.[19] The protocol was approved by the appropriate institutional review board for each site. Written informed consent was obtained for each subject.

Eligible men or women were 65 years old or older with self-reported UUI symptoms for 3 or more months, a mean of 2 to 15 UUI episodes, 8 or more micturitions per 24 hours on baseline 3-day bladder diary, and at least some moderate bladder related problem on the PPBC (Patient Perception of Bladder Condition)[20] who were determined to be vulnerable (at risk of deteriorating health) by a score of 3 or more on the VES-13 at screening (see Appendix).[21] UUI episodes were defined as voids that subjects rated with a score of 5 on the USS (Urinary Sensation Scale).[22] Subjects had to be capable of adequate mobility for independent toileting (could use cane or walker) and independent completion of bladder diaries and study related questionnaires.

Exclusion criteria were any condition contraindicating the use of fesoterodine; clinically significant hepatic disease or liver enzymes greater than 2 times the upper limit of normal; clinically significant renal disease and/or estimated creatinine clearance less than 30 ml per minute; neurological conditions that may specifically affect bladder function; previous surgery that might alter bladder function; advanced malignancy; clinically significant bladder outflow obstruction; PVR greater than 200 ml; predominant stress urinary incontinence; recurrent urinary tract infection; significant constipation; MMSE score less than 20;[23] behavioral interventions or electrical stimulation within 8 weeks; antimuscarinic medication use within 3 weeks; initiation or variable dose of tricyclic antidepressants, α-blockers, estrogens (within 4 weeks) or diuretics (within 2 weeks); an unstable medical condition; or average resting heart rate of 90 beats per minute or greater.

Subjects were randomized 1:1 to receive fesoterodine or matching placebo once daily for 12 weeks. The randomization schedule was generated, secured, distributed and stored by Pfizer Global Clinical Data Services. Subjects randomized to fesoterodine were initiated on the 4 mg dose. At the week 4 visit the dose could be increased to 8 mg based on discussion between the subject and investigator regarding treatment efficacy and tolerability. Subjects on a potent cytochrome P450 3A4 inhibitor were not allowed to increase the dose. Subjects who increased in dose to 8 mg could return to 4 mg at any time but could not increase again. Subjects in the placebo arm received sham dose escalation and de-escalation.

Subjects completed 3-day bladder diaries and the OAB-q (Overactive Bladder Questionnaire) at baseline and weeks 4 and 12,[24] the PPBC at screening and weeks 4 and 12,[20] and the OAB-S:C (OAB Satisfaction Questionnaire: Satisfaction with OAB Control Module) and OAB-S:GMS (OAB Satisfaction Questionnaire: Global Medication Satisfaction question) at week 12.[25] Bladder diaries included the times subjects arose and went to sleep and of every micturition, the sensation associated with