

Fesoterodine Dose Response in Subjects With Overactive Bladder Syndrome

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OBJECTIVES

To compare the efficacy of fesoterodine 4 mg versus 8 mg in treating subjects with overactive bladder (OAB) syndrome.

METHODS

This is a pooled analysis of data from 2 randomized placebo (PBO)-controlled phase III trials. Eligible subjects with frequency and urgency or urgency urinary incontinence (UUI) were randomized to PBO or fesoterodine 4 or 8 mg for 12 weeks. Subjects assessed efficacy using 3-day bladder diaries recording the time of each void, urgency, and incontinence episode. Endpoints included treatment response (based on a 4-point Treatment Benefit scale) and change from baseline in micturitions, UUI episodes, mean volume voided, urgency episodes, and continent days. We assessed tolerability and safety by evaluating adverse events, residual urine volume, laboratory parameters, and treatment withdrawals.

RESULTS

At the end of treatment, both doses of fesoterodine showed statistically significant improvements in all efficacy endpoints versus PBO ($P < 0.01$). These effects were seen 2 weeks after initiation of treatment (the earliest evaluation point) and were sustained throughout the treatment period. Fesoterodine 8 mg performed significantly better than fesoterodine 4 mg in improving all diary variables ($P < 0.05$) except micturition frequency, demonstrating a dose-response relationship. Adverse events reported more frequently with fesoterodine than with PBO included dry mouth, constipation, and urinary tract infection.

CONCLUSIONS

Both fesoterodine 4 and 8 mg are effective in improving OAB symptoms. The higher 8-mg dose provides additional benefit compared with the lower dose in improving most bladder diary variables, thus offering the possibility of dose flexibility and titration. UROLOGY 71: 839–843, 2008. © 2008 Elsevier Inc.

Many patients with overactive bladder (OAB) syndrome are successfully managed with antimuscarinic agents, but responses are variable.¹ Further therapeutic benefit might be achieved with higher doses; however, dose escalation has not become routine in clinical practice.² This may, in part, be because previous fixed-dose studies with the antimuscarinic agents darifenacin^{3,4} and solifenacin^{5,6} have failed to demonstrate a clear efficacy dose-response in parallel dosing studies. Any new therapeutic

agent that can demonstrate significantly improved efficacy and greater symptomatic relief at a higher dose would be beneficial.

Fesoterodine is a nonselective oral antimuscarinic agent that exerts its pharmacologic effects as a competitive muscarinic receptor antagonist. Fesoterodine acts as a prodrug; when administered, it is rapidly hydrolyzed by nonspecific esterases to the active metabolite, 5-hydroxymethyl tolterodine (5-HMT).⁷ After oral dosing, the parent compound is not detectable in plasma.⁷ The main active metabolite of fesoterodine, 5-HMT, is identical to the active metabolite of tolterodine; 5-HMT is formed from tolterodine by cytochrome P450 2D6-mediated oxidation in the liver.⁸ In phase I studies it has been demonstrated that fesoterodine is associated with a dose-dependent pharmacokinetic profile⁹ and low pharmacokinetic variability.¹⁰

The purpose of this pooled analysis was to evaluate the 2 doses of fesoterodine used in the phase III clinical studies (4 and 8 mg) for dose-dependent increases in efficacy as well as safety and tolerability in a larger population. The goal was to provide evidence to sup-

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Table 1. Baseline demographic and clinical characteristics*

Characteristic	PBO (n = 554)	Fesoterodine 4 mg (n = 554)	Fesoterodine 8 mg (n = 566)
Gender, % (n) women	78 (430)	78 (434)	80 (452)
Mean age, yr (range)	57 (19–88)	58 (19–86)	57 (20–91)
Ethnic origin, % (n)			
White	89 (494)	88 (490)	91 (514)
Black	5 (29)	5 (26)	4 (24)
Asian	2 (9)	1 (8)	1 (7)
Other	4 (22)	5 (30)	4 (21)
Time since OAB diagnosis, yr (SD)	9.8 (10.3)	9.1 (10.3)	10.1 (11.5)
Previous treatment for OAB, % (n)	50 (274)	48 (264)	50 (283)
Incontinent, % (n) [†]	76 (416)	80 (427)	81 (441)

FAS = full analysis set; OAB = overactive bladder; PBO = placebo; SD = standard deviation.

* Based on safety population (ie, all subjects who took ≥ 1 dose of medication).

[†] Based on FAS population.

port the practice of dose individualization in subjects with OAB.

MATERIAL AND METHODS

Study Design

This was a pooled analysis of data from 2 fixed-dose, multicenter, double-blind, placebo (PBO)-controlled trials with similar inclusion/exclusion criteria.^{11,12} Eligible subjects were randomized to PBO, fesoterodine 4 mg, or fesoterodine 8 mg, for 12 weeks. One trial also used tolterodine extended release 4 mg as an active comparator; those data are published elsewhere.¹¹

Subjects

Eligible subjects (18 years of age or older) included men and women with OAB syndrome for 6 or more months; this included urinary frequency (8 or more micturitions per 24 hours) and urinary urgency (6 or more episodes during the 3-day diary period) or UUI (3 or more episodes during the 3-day diary period). After the start of the trial, a protocol amendment was made to require UUI to ensure enrollment of a sufficient number of subjects with UUI (prespecified in the protocol to be 80% of each treatment group). The amended inclusion criterion required 3 or more UUI episodes to be recorded in the 3-day diary at the end of the placebo run-in for all remaining subjects.^{11,12} Subjects had to have at least moderate bladder problems on a 6-point Likert scale.¹³

Key exclusion criteria included the presence of lower urinary tract pathology that could, in the investigator's opinion, be responsible for urgency or incontinence (for example, significant stress incontinence, urolithiasis, interstitial cystitis, urothelial tumors); pelvic organ prolapse grade III or higher; clinically relevant bladder outlet obstruction; postvoid residual urine volume greater than 100 mL; polyuria (more than 3 L/24 hours); symptomatic or recurrent urinary tract infections; current treatment with antimuscarinic agents; a neurogenic cause of OAB symptoms; clinically relevant arrhythmia, unstable angina, or a QTcB interval greater than 500 ms; current treatment, or treatment within the past 4 weeks, with electrostimulation or bladder training during the past 4 weeks.^{11,12}

Efficacy Analysis

Efficacy was assessed using a 3-day bladder diary, which was completed before randomization and at 2, 8, and 12 weeks after initiating treatment. Subjects recorded the time of each

void, volume voided, urgency, and UUI episodes. Voided volumes were recorded on 1 day of the 3-day diary.

The primary endpoint in both trials was the change from baseline in the number of micturitions per 24 hours. Co-primary endpoints in both trials were change from baseline in the mean number of UUI episodes per 24 hours, and treatment response (a yes/no variable derived from a 4-point Treatment Benefit scale). Secondary efficacy endpoints included changes in mean volume voided (MVV) per micturition, mean number of daytime micturitions, mean number of nocturnal micturitions, continent days per week (data normalized from the 3-day bladder diary), and mean number of urgency episodes per 24 hours.

Statistical Analysis

We performed parametric analysis for continuous variables of the pooled data on all randomized subjects for whom baseline and double-blind treatment data were obtained (full analysis set [FAS]), using an analysis of covariance model with treatment and region as factors and baseline value as a covariate. We conducted nonparametric sensitivity analysis using the Wilcoxon rank sum test. Treatment response was analyzed using the asymptotic normal approximation method. In exploratory analyses, we calculated median percentage change from baseline to week 2 and week 12 for bladder diary endpoints, and conducted statistical hypothesis testing for secondary endpoints.

We applied a sequentially rejective closed-test procedure to the primary variables to adequately account for multiplicity. According to requirements of the U.S. Food and Drug Administration, the test procedure started with micturition frequency per 24 hours, and performed the test of fesoterodine 8 mg versus PBO for this variable, stepped down to the fesoterodine 4 mg versus PBO test in the event of statistical significance for the 8-mg dose group, and continued with the respective tests for the co-primary endpoint of number of UUIs per 24 hours if results for the micturition variable were significant for both doses.

We conducted safety analyses on all subjects who took at least 1 dose of trial medication after randomization (safety population). Demographic characteristics are also presented for this population.

RESULTS

Subjects

Table 1 presents the baseline demographics. Subjects reported a mean (\pm standard deviation [SD]) age of 57

Table 2. Primary and secondary efficacy endpoints at 2 weeks and end of treatment (EOT)

	Range of Mean Baseline Values		2 wk			EOT		
			PBO	FESO 4 mg	FESO 8 mg	PBO	FESO 4 mg	FESO 8 mg
Micturition frequency/24 h	12.0–12.2	LS mean change	−0.7	−1.0*	−1.3*	−1.0	−1.7*	−2.0*
		Median % change	−4.5	−8.3*	−10.7*	−10.0	−15.5*	−17.1*
		n	538	522	537	545	532	543
UUI episodes/24 h	3.7–3.9	LS mean change	−0.6	−1.5*	−1.7*	−1.1	−1.9*	−2.3*†
		Median % change	−23.0	−43.2*	−58.3*†	−42.9	−75.0*	−83.3*†
		n	410	422	437	416	427	441
Treatment response	—	% yes	45	61*	67*†	49	69*	77*†
MVV, mL	155–156	n	532	514	532	545	532	543
		LS mean change	7.2	18.4*	33.3*†	9.0	22.2*	33.6*†
Urgency episodes/24 h	11.4–11.8	n	529	518	532	539	531	540
		LS mean change	−0.7	−1.2*	−1.6*†	−0.9	−2.0*	−2.3*
Continent days/wk†	0.7–0.8	Median % change	−4.1	−8.8	−12.1*†	−7.7	−16.7*	−18.6*
		n	538	522	537	545	532	543
		LS mean change	0.8	1.5*	2.0*†	1.8	2.6*	3.1*†
		n	410	422	437	416	427	441

FESO = fesoterodine; LS = least square; MVV = mean volume voided; PBO = placebo; UUI = urgency urinary incontinence.

* $P < 0.01$ versus PBO.

† $P < 0.05$ versus fesoterodine 4 mg.

‡ Extrapolated from 3-day diary data.

(± 13) years, and most were women (79%) and white (90%), with 76% to 81% of subjects reporting incontinence at baseline. The mean time since first diagnosis or onset of OAB was 8 to 9 years. Approximately half of the subjects had previously received pharmacotherapy for their OAB. Only 5% to 8% of subjects in any group had been diagnosed with OAB for less than 1 year before enrollment; therefore, the population in this trial was primarily composed of subjects with long-term, established OAB.

Efficacy

By the end of treatment, both fesoterodine-treated groups (4 and 8 mg) showed statistically significant improvements in primary and secondary efficacy endpoints from baseline, including micturition frequency per 24 hours, UUI episodes per 24 hours, treatment response, MVV per micturition, urgency episodes per 24 hours, and continent days per week versus PBO ($P < 0.01$) (Table 2). These effects were seen at the first clinical evaluation, 2 weeks after initiation of treatment, and were sustained throughout the study (Fig. 1). Fesoterodine 8 mg performed significantly better than fesoterodine 4 mg in improving all diary variables ($P < 0.05$) with the exception of micturition frequency, which showed a numerical advantage (change from baseline -1.97 and -1.74 for fesoterodine 8 and 4 mg, respectively [$P = 0.184$]).

Safety and Tolerability

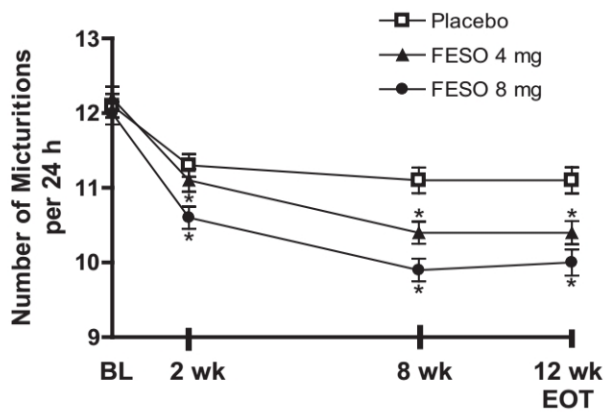
The most common treatment-emergent adverse events (2% or greater in any fesoterodine group) are listed in

Table 3 and include dry mouth, constipation, urinary tract infection, and headache; the majority of these events were mild to moderate in nature (Table 3).

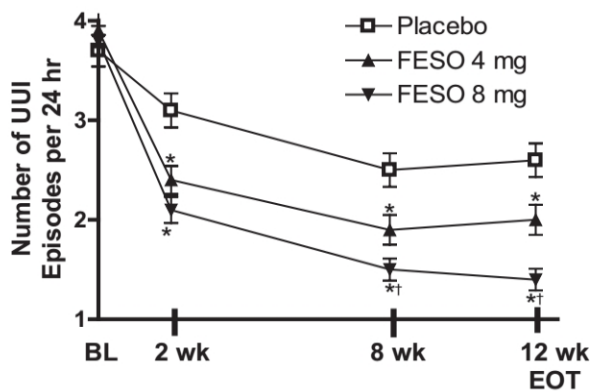
Overall, 5.2% of subjects (87 of 1674) discontinued the study prematurely owing to an adverse event (AE): PBO, 3.4% (19 of 554); fesoterodine 4 mg, 4.9% (27 of 554); and fesoterodine 8 mg, 7.2% (41 of 566) during the treatment phase. No single AE resulted in withdrawal of 1% or greater of subjects in any treatment group. Among the reasons for discontinuation were urinary retention (defined by investigator and not necessarily requiring intervention), which occurred in 1% (6 of 554) of subjects in the fesoterodine 4 mg group and 1% (8 of 566) of subjects in the fesoterodine 8 mg group, and led to discontinuation in 8 subjects. Similarly, discontinuation rates from dry mouth and constipation were low (less than 1%), with 9 and 3 subjects (of 1120 subjects receiving fesoterodine) withdrawing, respectively.

COMMENT

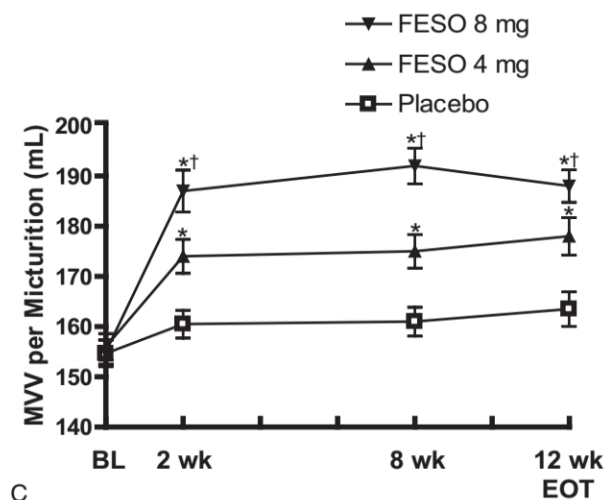
Fesoterodine significantly improved OAB symptoms as early as 2 weeks after initiation of treatment, the earliest evaluation point included in the trials, compared with PBO. Fesoterodine 8 mg was significantly more efficacious than the 4-mg dose in improving UUI episodes, urgency episodes, bladder capacity (assessed as MVV per micturition), continent days, and treatment response. This dose–response relationship is rare in parallel-group studies of antimuscarinics that offer multiple doses. Only oxybutynin has shown statistically significant differences



A



B



C

Figure 1. (A) Time course of micturition frequency with PBO or fesoterodine 4 or 8 mg. Data shown are mean \pm SEM at baseline, at 2 and 8 weeks, and at end of treatment (12 weeks, EOT). * P < 0.05 versus PBO; † P < 0.05 versus fesoterodine 4 mg. (B) Time course of number of UUI episodes with PBO or fesoterodine 4 or 8 mg. Data shown are mean \pm SEM at baseline, at 2 and 8 weeks, and at end of treatment (12 weeks, EOT). * P < 0.05 versus PBO; † P < 0.05 versus fesoterodine 4 mg. (C) Time course of MVV per micturition with PBO or fesoterodine 4 or 8 mg. Data shown are mean \pm SEM at baseline, at 2 and 8 weeks, and at end of treatment (12 weeks, EOT). * P < 0.05 versus PBO; † P < 0.05 versus fesoterodine 4 mg. BL = baseline; PBO = placebo.

Table 3. Treatment-emergent adverse events at end of study ($\geq 2\%$ of subjects receiving fesoterodine)

Adverse Event	PBO (N = 554) % (n)	Fesoterodine	Fesoterodine
		4 mg (N = 554) % (n)	8 mg (N = 566) % (n)
Dry mouth	7 (39)	19 (104)	35 (196)
Mild	5 (27)	15 (84)	22 (126)
Moderate	2 (11)	3 (16)	9 (53)
Severe	<1 (1)	<1 (4)	3 (17)
Constipation	2 (11)	4 (23)	6 (34)
Mild	1 (8)	2 (14)	3 (18)
Moderate	<1 (1)	1 (8)	2 (14)
Severe	<1 (2)	<1 (1)	<1 (2)
Urinary tract infection	3 (17)	3 (18)	4 (24)
Mild	2 (12)	2 (11)	3 (15)
Moderate	1 (5)	1 (7)	1 (8)
Severe	0	0	<1 (1)
Headache	4 (23)	4 (24)	3 (15)
Mild	3 (19)	3 (15)	2 (9)
Moderate	<1 (3)	1 (6)	1 (5)
Severe	<1 (1)	<1 (3)	<1 (1)
Lacrimal disorder	0	1 (8)	4 (21)
Dyspepsia	<1 (3)	2 (9)	2 (13)
Dry throat	<1 (2)	1 (5)	2 (13)
Upper respiratory tract infection	2 (12)	2 (14)	2 (10)
Nasopharyngitis	2 (14)	3 (18)	1 (7)

PBO = placebo.

among the 15-mg dose and the 2 lower doses (5 and 10 mg) for reduction of UUI episodes and MVV per micturition.¹⁴ Dose separation has not been demonstrated for efficacy outcomes with darifenacin,^{3,15} solifenacin,⁵ or tolterodine.^{16–18} The reason for the fesoterodine dose response may lie in its pharmacokinetic and pharmacologic profile. Unlike tolterodine, darifenacin, or solifenacin, which are metabolized in the liver to produce active metabolites,¹⁹ hepatic enzymes are not involved in the conversion of fesoterodine to its active metabolite. Instead, this conversion is mediated by nonspecific esterases, which are not known to exhibit interindividual variability, nor to be involved in drug interactions. In addition, given the ubiquitous localization of nonspecific esterases, intersubject variability in the formation of the active metabolite was demonstrated to be very low.¹⁰

Similar to other antimuscarinic agents, such as oxybutynin, solifenacin, and darifenacin, adverse events with fesoterodine, such as dry mouth, increased in a dose-dependent fashion. Although adverse events were expected based on the antimuscarinic mechanism of action, the relative contribution of typical antimuscarinic adverse events for any antimuscarinic agent most likely results from its unique balance of activity at different muscarinic receptor subtypes.¹ For example, the incidence of dry mouth increased from 19% (fesoterodine 4 mg) to 35% (fesoterodine 8 mg; PBO, 7%) with most cases being mild to moderate in nature. This incidence rate is somewhat higher than that reported for solifena-

cin²⁰ (5 mg, 11%; 10 mg, 28%; PBO, 4%) and is lower than that reported for oxybutynin¹⁴ (5 mg, 56%; 10 mg, 68%; 15 mg, 70%) and darifenacin¹⁵ (7.5 mg, 23%; 15 mg, 40%; PBO, 8%).

Interestingly, compared with other antimuscarinic agents, the incidence of constipation with fesoterodine was relatively low, increasing from 4% with the 4-mg dose to 6% with the 8-mg dose. In comparison, constipation was 4% to 5% with oxybutynin (for 5, 10, or 15 mg),¹⁴ 5% and 13% with solifenacin (5 and 10 mg, respectively),²⁰ and 16% and 25% with darifenacin (7.5 and 15 mg, respectively).¹⁵ In the gastrointestinal tract, as in the bladder, M₂ receptors outnumber M₃ receptors approximately 4 to 1²¹; the M₃ subtype mediates cholinergic stimulation of gastrointestinal motility.²² The low incidence of constipation with fesoterodine may be attributed to its nonselective receptor binding profile, which is in contrast to the M₃ selectivity of darifenacin.^{23,24}

Pooled data from these two phase III trials have thus demonstrated that fesoterodine has the ability to significantly reduce OAB symptoms, including urgency and UUI, in a dose-dependent fashion. The 8-mg dose provides significant additional benefit in improving most bladder diary variables compared with the lower dose and allows for dose titration and individualization in subjects with OAB. This allows subjects to achieve a more optimal balance between treatment efficacy and tolerability.

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