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ORIGINAL ARTICLE

Do patient characteristics predict which patients with overactive bladder benefit from a higher fesoterodine dose?

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Abstract

Introduction and hypothesis We sought to determine whether baseline characteristics predict which overactive bladder (OAB) patients benefit from fesoterodine 8 mg versus 4 mg.

Methods In double-blind, placebo-controlled, flexible-dose trials, baseline characteristics of OAB patients with ≥ 1 urgency urinary incontinence (UUI) episodes/24 h who escalated from fesoterodine 4 mg to 8 mg were evaluated. Possible dose-escalation predictors (age; sex; previous antimuscarinic use; UUI, micturitions, and urgency episodes/24 h; race; body mass index; time to dose escalation; OAB duration) were compared in escalators versus non-escalators. Patients from fixed-dose trials with dose-escalator characteristics were identified (matched dose-escalator sample) to assess changes from baseline with fesoterodine 4 mg, 8 mg, and placebo.

Results In flexible-dose trials, significant predictors of fesoterodine dose escalation were younger age (≤ 65.8 years), greater number of baseline micturitions (≥ 13.1) and urgency episodes/24 h (≥ 10.9), greater OAB duration (≥ 9.1 years), and more frequent previous antimuscarinic use (58.3%), but not baseline UUI episodes/24 h. In the matched dose-escalator sample (fesoterodine 4 mg: $n = 215$; 8 mg: $n = 198$; placebo: $n = 217$), change from baseline in UUI episodes significantly improved with fesoterodine 8 mg versus 4 mg ($P = 0.043$) and with both doses versus placebo ($P < 0.001$). Dry mouth and constipation rates were higher with fesoterodine 8 mg.

Conclusions Dose-escalator patients had a significantly greater UUI response with fesoterodine 8 mg versus 4 mg. Given the potential for adverse events, fesoterodine 4 mg is recommended to start; however, patients with UUI and identified predictors may benefit from initial treatment with fesoterodine 8 mg or rapid dose escalation.

Keywords Urinary bladder, overactive · Urinary incontinence, urge · Fesoterodine · Dose-response relationship, drug · Randomized-controlled trials

Introduction

Overactive bladder (OAB) symptoms, including urgency urinary incontinence (UUI), are prevalent and highly bothersome and negatively impact health-related quality of life [1, 2]. Patients with OAB symptoms, including UUI, are more bothered by their symptoms than those with OAB without UUI and report significantly deteriorated health-related quality of life [3, 4]. Antimuscarinic agents are a recommended pharmacologic treatment for OAB [5], but treatment response and tolerability can vary by drug, dose, and individual patient. In clinical practice, healthcare practitioners can adjust the antimuscarinic dose and switch from one antimuscarinic to another to increase the efficacy and/or reduce adverse effects in individual patients with OAB [6, 7]. Dose adjustment is only possible with antimuscarinics that are available in different doses and demonstrate a dose-response effect. The 12-week, double-blind, placebo-controlled, fixed-dose, EIGHT trial demonstrating the superior efficacy of

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fesoterodine 8 mg over fesoterodine 4 mg or placebo with respect to UUI episodes, micturitions, urgency episodes, and patient-reported health-related quality of life confirmed the dose-response effect of fesoterodine [8]. A dose-response effect for the reduction of OAB symptoms using a superiority design has not been demonstrated for any other OAB treatment.

Flexible-dose studies are thought to reflect real-world clinical practice, because the drug dose can be increased in individual patients when their treatment response is insufficient with a lower dose. In four double-blind, placebo-controlled, flexible-dose trials [9–12], 51% to 63% of patients with OAB initially treated with fesoterodine 4 mg opted to increase their dose to 8 mg [13]. Data from these trials indicated that both fesoterodine 4 mg and 8 mg provide a significant treatment benefit versus placebo with a dose-response effect. A post hoc analysis of data from the flexible-dose trial reported by Dmochowski et al. [9] showed that patients who dose escalated to 8 mg (274 of 438 patients, 62.6%) at week 2 had a statistically significantly greater number of micturitions and urgency episodes at baseline versus non-escalators ($n = 164$; $P < 0.001$) and significantly less improvement in these outcomes ($P < 0.001$) at week 2 (before dose escalation) versus non-escalators [14]. Additional studies have evaluated baseline treatment-related factors leading to fesoterodine dose escalation in a single flexible-dose study [15] and compared effectiveness of fesoterodine 8 mg versus 4 mg in two fixed-dose studies according to number of baseline UUI episodes/24 h [16].

In the current study, we examined the differences between fesoterodine escalators and non-escalators across multiple flexible- and fixed-dose studies. Our hypothesis was that baseline characteristics of dose escalators can be identified that will help predict which patients will achieve greater efficacy with fesoterodine 8 mg versus 4 mg.

Materials and methods

Identifying baseline characteristics of fesoterodine dose escalators in flexible-dose trials

Post hoc analyses of pooled data from four 12-week, double-blind, placebo-controlled, flexible-dose trials [9–12] of fesoterodine were conducted to identify baseline characteristics of OAB patients treated with fesoterodine (fesosterodine fumarate, Toviaz®, Pfizer, Inc.) ≥ 1 UUI episodes (Urinary Sensation Scale score = 5)/24 h at baseline who opted to escalate their fesoterodine dose from 4 mg to 8 mg (at week 2 or 4) and completed the trial (Analysis 1; Fig. 1). Possible predictors of dose escalation [age; sex; previous antimuscarinic use (yes vs. no); UUI episodes/24 h, micturitions/24 h, and urgency episodes (Urinary Sensation Scale score ≥ 3)/24 h at baseline; race (white vs. other); body mass index; time to dose escalation; OAB duration] were assessed by comparing escalators versus non-escalators in a univariate and a step-wise multivariate logistic regression analysis. For the univariate analysis, a paired t test was used for continuous variables, and a McNemar test was used for proportions at a two-sided 5% significance level. For the step-wise multivariate logistic regression analysis, variables demonstrating a 5% significance level were retained in the model.

Matching patients in fixed-dose trials to dose escalators in flexible-dose trials

Next, we tested the hypothesis that patients with similar baseline characteristics to those of fesoterodine dose escalators would experience greater efficacy and a comparable adverse event profile with fesoterodine 8 mg versus 4 mg. Patients in fixed-dose studies provided the opportunity to compare efficacy and safety outcomes with the two doses of fesoterodine in patients who were dose escalators in the flexible-dose trials. First, we identified a matched dose-escalator sample of patients from the two pivotal double-blind, placebo-controlled, fixed-dose (4 mg or 8 mg) fesoterodine trials [17, 18] using propensity score analysis (Analysis 2; Fig. 1). The propensity score [19] represents the probability of patients in the fixed-dose trials having the distribution of baseline characteristics similar to those of dose escalators in the flexible-dose trials. Matching without replacement was applied so that each dose escalator in the flexible-dose trials was matched to the fixed-dose patient with the closest propensity score. The quality of the propensity scores estimated were evaluated by comparing the distributions of the propensity scores across the fixed-dose patients and dose escalators and comparing the distributions of each covariate across the two groups. The characteristics of the matched dose-escalator sample from the fixed-dose trials were compared with those of dose escalators from the flexible-dose trials, with a non-significant p value indicating a comparable mean or proportion between the two patient populations and effective matching of patient characteristics.

Assessing fesoterodine efficacy and safety in the matched dose-escalator sample

Efficacy variables (i.e., UUI episodes/24 h, micturitions/24 h, and urgency episodes/24 h) for the matched dose-escalator sample from the two fixed-dose trials were analyzed with an analysis of covariance model with terms for baseline value, treatment, study, and treatment-by-baseline value interaction at the 5% level of significance (Analysis 3; Fig. 1). The least-squares mean changes from baseline to week 12 in each efficacy variable were compared for patients treated with fesoterodine 8 mg versus fesoterodine 4 mg and for each fesoterodine dose versus placebo. Treatment-emergent adverse events (all cause) were descriptively summarized for each treatment group.

Ethics

The studies included in this analysis were all conducted in accordance with the International Conference on

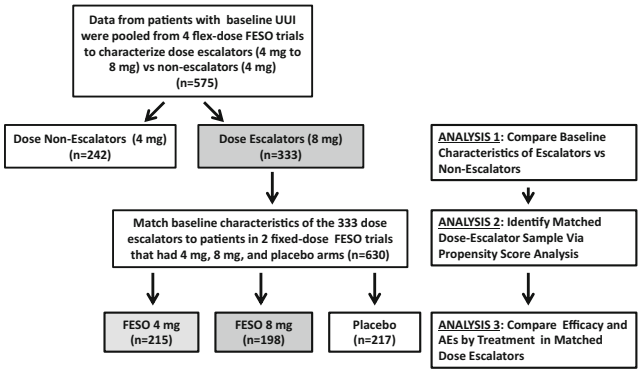

Fig. 1 Flow chart of post hoc analyses. FESO = fesoterodine; UUI = urgency urinary incontinence

Harmonisation guidelines on Good Clinical Practice and the Declaration of Helsinki. Protocols were approved by ethics committees and/or institutional review boards, and all subjects provided written informed consent before study participation [9–12, 17, 18]. Informed consent forms for each of the flexible-dose studies and one of the two fixed-dose studies explicitly stipulated that data collected during the study may be used for future studies such as the current analysis [9–12, 17]. Data from the remaining fixed-dose study, which was a phase III trial that began in 2003 [18], have previously been used in multiple other post hoc analyses [16, 20, 21].

Results

Analysis 1

In four double-blind, placebo-controlled, flexible-dose fesoterodine trials, significant (univariate $P < 0.001$, unless otherwise specified) predictors of dose escalation in 333 OAB patients with ≥ 1 UUI episodes/24 h at baseline who escalated to the fesoterodine 8-mg dose versus 242 non-escalators (remained on the fesoterodine 4-mg dose) were: baseline age (65.8 years for escalators versus 71.0 years for non-escalators), micturitions/24 h at baseline (13.1 versus 11.0), urgency episodes/24 h at baseline (10.9 versus 9.2), OAB duration (9.1 versus 7.1 years; $P = 0.004$), and previous antimuscarinic use (58.3% versus 22.3%). Importantly, the number of baseline UUI episodes (3.1 versus 3.4)/24 h was not a significant predictor of dose escalation. Micturitions/24 h at baseline ($P = 0.016$) and previous antimuscarinic use ($P = 0.008$) were the only independent predictors of dose escalation in a step-wise multivariate analysis.

Analysis 2

Using nine baseline characteristics of dose escalation in a propensity score analysis, a matched sample of 630 patients (fesoterodine 4 mg: $n = 215$; fesoterodine 8 mg: $n = 198$; placebo: $n = 217$) with the chararacteristics of dose escalators was identified from the two fixed-dose pivotal fesoterodine trials (Table 1). Data were distributed normally for continuous baseline characteristics. For each of the baseline characteristics, the non-significant *P*-value indicated a comparable patient characteristic in patients from the fixed-dose trials compared with the dose escalators from the flexible-dose trials.

Analysis 3

For the 630 patients in the matched dose-escalator sample, the change from baseline to week 12 in UUI episodes was significantly improved with fesoterodine 8 mg versus fesoterodine 4 mg ($P = 0.043$; Table 2). Thus, the baseline characteristics identified in Analysis 1 did predict a greater improvement in UUI episodes with the 8-mg dose versus the 4-mg dose of fesoterodine at week 12. The comparisons between fesoterodine 8 mg and fesoterodine 4 mg versus placebo also

Table 1 Patient characteristics after matching patients in fixed-dose fesoterodine trials to dose escalators from fesoterodine flexible-dose trials

Characteristic	Pivotal trials: matched dose-escalator sample ($N = 630$)	Dose escalators from 4 flexible-dose trials ($N = 333$)	*P* value*
Mean age, years (SD)	63.1 (11.9)	65.8 (12.9)	0.889
Mean BMI, kg/m^2 (SD)	30.4 (7.3)	31.1 (7.5)	0.632
Mean UUI episodes/24 h at BL (SD)	3.4 (3.4)	3.1 (2.3)	0.162
Mean micturitions/24 h at BL (SD)	12.6 (4.0)	13.1 (3.1)	0.807
Mean urgency episodes/24 h at BL (SD)	11.3 (4.4)	10.9 (3.5)	0.995
Duration of OAB, years (SD)	9.6 (11.0)	9.1 (8.8)	0.163
Race, white, %	89.5	90.1	0.524
Female, %	81.7	85.6	0.658
Previous antimuscarinic use, %	55.9	58.3	0.939

*P values from paired t test for continuous variables or McNemar test for proportions at the 5% level of significance, with a non-significant P value indicating a comparable mean or proportion between the two patient samples

BL baseline, *BMI* body mass index, *OAB* overactive bladder, *SD* standard deviation, *UUI* urgency urinary incontinence

were statistically significant (each $P < 0.001$). The improvements from baseline to week 12 in micturitions/24 h and urgency episodes/24 h with fesoterodine 8 mg versus 4 mg were not statistically significant ($P = 0.159$ and $P = 0.170$, respectively); statistical significance was demonstrated for fesoterodine 8 mg and fesoterodine 4 mg versus placebo (each $P < 0.001$).

The most frequent treatment-emergent adverse events (all causes) in the matched dose-escalator sample were dry mouth (fesoterodine 4 mg: 19.5%; fesoterodine 8 mg: 37.9%; placebo: 6.9%) and constipation (fesoterodine 4 mg: 3.3%; fesoterodine 8 mg: 7.6%; placebo: 2.3%; Table 3). The incidence of each of these adverse events was related to the fesoterodine dose, with a higher incidence in patients treated with fesoterodine 8 mg versus 4 mg.

Discussion

The current post hoc analyses were conducted to test the hypothesis that patient baseline characteristics can help healthcare providers decide which individual patients with OAB are more likely to achieve additional symptom relief with fesoterodine 8 mg versus 4 mg. The results suggested that a lower mean age (66 versus 71 years), more severe (≥ 13) micturitions/24 h, more severe (≥ 11) urgency episodes/24 h, greater (≥ 9 years) OAB duration, and patients who predominantly (58%) had previous antimuscarinic use at baseline predict a significantly better UUI response with fesoterodine 8 mg versus 4 mg. Interestingly, the number of UUI episodes/24 h at baseline was not a significant variable predicting a better UUI response with fesoterodine 8 mg versus 4 mg. The identified baseline characteristics of dose escalators did not significantly differentiate between the two fesoterodine doses for improvements in micturitions/24 h or urgency episodes/24 h. Overall, the results suggest that patient baseline characteristics may have a role in predicting which patients are more likely to have a better UUI response with fesoterodine 8 mg versus 4 mg. Furthermore, the change from baseline in UUI episodes/24 h may represent the most meaningful outcome for assessing treatment response in patients with OAB and UUI.

The incidence rates of dry mouth and constipation for the matched dose-escalator sample in the current analysis were higher in patients receiving fesoterodine 8 mg than in those receiving fesoterodine 4 mg. In contrast, Staskin et al. [14] reported in a post hoc analysis of the flexible-dose study by Dmochowski et al. [9] that the incidence rates of dry mouth and constipation were generally higher for non-escalators versus escalators both before and after fesoterodine dose escalation [14]. Thus, it was suggested that the decision to dose escalate was related to a patient's sensitivity to the drug, with non-escalators more sensitive to fesoterodine than escalators [14]. The results of the present analysis for the matched dose-escalator sample from the fixed-dose studies did not replicate these findings with respect to adverse events, as we found that the incidence rates of common adverse events were greater with fesoterodine 8 mg than 4 mg. The reasons for this discrepancy are unclear.

Other studies of possible predictors of the optimal dose of fesoterodine include a post hoc analysis by Cardozo et al. that evaluated pooled data from the two pivotal fixed-dose trials [17, 18] to evaluate whether the severity of UUI episodes at baseline predicts which patients with OAB and UUI would benefit from the 8-mg dose [16]. For this analysis, 1327 patients with UUI at baseline and treated with fesoterodine 4 mg, fesoterodine 8 mg, or placebo were stratified into baseline UUI tertiles [> 0 to < 2 (mean: 1); 2 to < 4 (mean: 3); or ≥ 4 (mean: 7) UUI episodes/24 h]. At week 12, the overall patient population had significantly greater improvements in UUI episodes with fesoterodine 4 mg and 8 mg versus placebo. Improvements were significantly greater with fesoterodine

Table 2 Efficacy outcomes in the matched dose-escalator sample (N = 630) from fixed-dose trials

Pivotal trials: matched dose-escalator sample-ANCOVA*	FESO 4 mg ($n = 215$)	FESO 8 mg ($n = 198$)	PBO (n = 217)
Mean UUI episodes/24 h at BL	3.3	3.5	3.3
Change from BL to week 12, LS mean	−1.6	−2.1	−0.7
P value: FESO vs. PBO	< 0.001	< 0.001	
P value: FESO 8 mg vs. FESO 4 mg		0.043	
Mean micturitions/24 h at BL	12.8	12.4	12.7
Change from BL to week 12, LS mean	−2.0	−2.5	−1.0
P value: FESO vs. PBO	< 0.001	< 0.001	
P value: FESO 8 mg vs. FESO 4 mg		0.159	
Mean urgency episodes/24 h at BL	11.5	11.2	11.4
Change from BL to week 12, LS mean	−1.9	−2.4	−0.3
P value: FESO vs. PBO	< 0.001	< 0.001	
P value: FESO 8 mg vs. FESO 4 mg		0.170	

*P values based on ANCOVA, with terms for study, treatment, baseline value, and treatment-by-baseline value interaction, at the 5% level of significance

ANCOVA analysis of covariance, *BL* baseline, *FESO* fesoterodine, *LS* least squares, *PBO* placebo

Table 3 Treatment-emergent adverse events (all causalities) in matched dose-escalator sample (N = 630) from fixed-dose trials

Adverse event, n (%)*	FESO 4 mg (n = 215)	FESO 8 mg (n = 198)	PBO (n = 217)
Dry mouth	42 (19.5)	75 (37.9)	15 (6.9)
Constipation	7 (3.3)	15 (7.6)	5 (2.3)
Urinary tract infection	9 (4.2)	9 (4.5)	8 (3.7)
Dry eye	3 (1.4)	7 (3.5)	0
Headache	13 (6.0)	3 (1.5)	11 (5.1)

*Adverse events occurring in ≥ 3% of patients in any treatment group
FESO fesoterodine, *PBO* placebo

8 mg versus 4 mg, but this was only true for patients with ≥ 2 UUI episodes/24 h at baseline. The incidence rates of dry mouth (fesoterodine 4 mg: 19%; fesoterodine 8 mg: 35%; placebo: 8%) and constipation (fesoterodine 4 mg: 5%; fesoterodine 8 mg: 6%; placebo: 2%) were dose related, but not related to the number of UUI episodes at baseline [16]. Our current results in patients with a baseline mean of ≥ 3 UUI episodes/24 h support the finding that relief of UUI episodes in patients with ≥ 2 UUI episodes/24 h at baseline is more responsive to fesoterodine 8 mg than 4 mg and that incidence rates of dry mouth and constipation are dose related.

Cardozo et al. also assessed factors associated with dose escalation in a 12-week, open-label, flexible-dose fesoterodine study in which 59% (195/331) of patients with OAB increased their fesoterodine dose from 4 mg to 8 mg at week 4, primarily because of an insufficient clinical response [15]. A smaller change from baseline in micturitions/24 h and a greater severity of patient-reported bladder problems (i.e., Patient Perception of Bladder Condition response) at week 4 were significantly associated with the decision to dose escalate; age, sex, body mass index, previous antimuscarinic use, micturitions at baseline, UUI status, and OAB duration were not. Our current results confirm that micturitions/24 h, whether at baseline or in terms of the change following treatment with fesoterodine 4 mg, is a significant predictor of the decision to increase the dose of fesoterodine. Combining results from the study by Cardozo et al. [15] and the current analysis identified only three factors (i.e., micturitions/24 h, previous antimuscarinic use, and patient perception of bladder-related problems) as independent predictors of fesoterodine dose escalation. Treatment expectations and goals, together with various psychological factors (e.g., risk-taking tendencies) of individual patients, may need to be included in the decision-making model.

While the analyses described above, as well as an additional flexible-dose study in the elderly, considered data from one or two studies [11, 14–16], the current analysis included data from four separate flexible-dose studies. Additionally, data from two fixed-dose studies were used to confirm that the 8-mg dose was more effective in patients with the baseline dose-escalator characteristics identified. Differences between findings from the current analysis and those from other studies may be explained by variations in sample sizes and study and/or participant characteristics. Nevertheless, the greater number of studies included in the current analysis suggest that the factors identified, and particularly those that were significant predictors of dose escalation in multivariate analysis, may be more reflective of the general population with OAB; the current analysis thus serves as an important clinical decision-making tool.

Possible limitations of the present results include that they were based on post hoc analyses of prospective trial data. The prediction of which patients may benefit from a higher dose of fesoterodine appears complicated. Additional unknown patient characteristics or psychological factors that affect the decision to dose escalate may play a role or interact with the variables evaluated; in clinical studies, individual investigators may even influence this decision. Additonally, the current analysis evaluated previous use of antimuscarinic drugs as a binary factor without regard to the number of previous drugs used; the number of drugs used may be important in identifying OAB refractory to antimuscarinics. Importantly, the patients in the fixed-dose trials were randomized to fesoterodine 4 mg or 8 mg, whereas all patients in the flexible-dose trials were initially treated with 4 mg before they could opt for dose escalation. These differences in study design may explain the differences observed in the incidences of adverse events with 8 mg versus 4 mg in the flexible-dose and fixed-dosed fesoterodine trials. While it would be beneficial to predict which patients would benefit from fesoterodine dose escalation, given the higher rates of dry mouth and constipation observed with the 8-mg dose, we recommend that all patients start at 4 mg and escalate as needed to potentially avoid discontinuation due to adverse events. Additional studies to examine predictors of antimuscarinic treatment response are warranted to provide healthcare practitioners with additional guidance on maximizing OAB symptom relief in individual patients.

Conclusions

Although we used a complex research model, our goal was to define a practical approach for healthcare providers to determine which patients with OAB would derive benefit from a higher dose of fesoterodine. The identified dose-escalator patients (i.e., patients whose baseline characteristics match those of patients who opted to escalate their fesoterodine dose from 4 mg to 8 mg) had a significantly greater UUI response with fesoterodine 8 mg versus 4 mg. Characteristics of patients who benefit from higher dose fesoterodine included younger age, greater number of micturitions/24 h, more severe urgency episodes/24 h, longer duration of OAB, and prior antimuscarinic

use. Given the greater risk of adverse events (dry mouth, constipation) with the 8-mg dose, the recommended approach for healthcare practitioners is to start patients with OAB on the 4-mg dose of fesoterodine and, if needed, escalate the dose to 8 mg to achieve additional symptom relief. However, patients with UUI and identified predictors may benefit from initial treatment with fesoterodine 8 mg or rapid escalation (after approximately 4 weeks) from 4 mg to 8 mg.

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Compliance with ethical standards

Conflicts of interest H. Goldman is a consultant for Pfizer, Allergan, Medtronic, and Axonics and was previously a consultant for Astellas. M. Oelke is a consultant for and/or has received honoraria or travel expenses from Apogepha, Astellas, Duchesnay, and Pfizer. S. Kaplan is a consultant for Pfizer. T. Kitta has no disclosures. E. Mangan is a former employee of Pfizer Inc. D. Russell, D. Arumi, M. Carlsson, and F. Ntanios are employees of Pfizer Inc.

Summary statement This study was sponsored by Pfizer Inc., and Pfizer employees participated in the analysis plan, data analysis, and manuscript preparation.

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