

Treatment Satisfaction with Flexible-dose Fesoterodine in Patients with Overactive Bladder who were Dissatisfied with Previous Anticholinergic Therapy: A Multicenter Single-Arm Clinical Study

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Purpose: We investigated treatment satisfaction with flexible-dose fesoterodine in patients with overactive bladder (OAB) who were dissatisfied with previous anticholinergic therapy.

Materials and Methods: The subjects were prescribed fesoterodine 4 mg for 4 weeks and fesoterodine 4 mg or 8 mg for another 8 weeks. The primary end point of this study was patients' satisfaction after 12 weeks of fesoterodine treatment on a five-point Likert scale. Secondary end points included a change in the number of daytime micturition, urgency incontinence episodes, urgency episodes, and nocturnal micturition in a -24hour period from baseline to final assessment.

Results: Overall, 84 patients were assigned to the treatment group in this study and 63 patients completed the -12week treatment course. A final fesoterodine dose of 4 mg and 8 mg was used by %71.4) 45) and %28.6) 18) patients, respectively. The satisfaction and dissatisfaction rates at 12 weeks were %69.9 and %14.2, respectively. Mean changes in the daytime micturitions (4.72 ± 9.73 vs. 2.86 ± 7.76), urgency episodes (5.68 ± 7.73 vs. ± 3.71 4.09), and nocturnal micturitions (1.36 ± 2.13 vs. 1.12 ± 1.68) in 24 hours improved significantly with flexible-dose fesoterodine treatment ($P < .05$). Most adverse events were mild and none were severe.

Conclusion: The flexible dose fesoterodine represents an alternative treatment modality in patients with OAB who are dissatisfied with previous anticholinergic therapy in Korea.

Keywords: fesoterodine; overactive bladder; patient satisfaction

INTRODUCTION

Overactive bladder (OAB) is defined as a syndrome that causes urgency (with or without urge incontinence), frequency, and nocturia.⁽¹⁾ The overall prevalence of OAB is approximately 16% in the USA and six European countries (Sweden, France, Spain, Italy, Germany, and the United Kingdom). The prevalence of the syndrome does not differ by sex even though the severity and expressed symptoms do.^(2,3) The overall prevalence of OAB in Korea has been reported to be approximately 12% and increases with age.⁽⁴⁾ Although anticholinergics are considered the mainstay of treatment for OAB⁽⁵⁾, their variable efficacy and poor compliance due to adverse effects such as dry mouth, constipation, and even cognitive impairment lead to low patient satisfaction.^(6,7) As a result, physicians switch

drugs or modify the dose when patients are dissatisfied with previous anticholinergic therapy.

Previous studies have demonstrated that fesoterodine at dosages of 4 mg or 8 mg once daily significantly improved OAB symptoms.^(8,9) Furthermore, the availability of the flexible doses of fesoterodine provides an opportunity to maintain an optimal balance between benefits and risks in patients.⁽¹⁰⁾ Recent data has shown that flexible-dose fesoterodine is associated with a high rate of patient treatment satisfaction, produced significant improvements in voiding diary variables and negative symptoms, and resulted in a greater health-related quality of life.⁽¹¹⁾ Several studies also reported the efficacy of switching anticholinergic therapy, including to fesoterodine, when patients were dissatisfied with previous anticholinergics.⁽¹¹⁻¹³⁾ However, there have been

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Table 1. Demographic and baseline parameters

Parameters	Patients (n = 63)
Age, years	59.1 ± 13.3
Range	26-82
Mean duration for suffering from OAB, months	42.6 ± 37.8
12 months or less	15 (23.8)
12 to 36 months	25 (39.7)
Over 36 months	23 (36.5)
Somewhat dissatisfied with prior anticholinergics	47 (74.6%)
Very dissatisfied with prior anticholinergics	16 (25.4%)

Data are presented in the format of mean ± standard deviation or n (%).

Abbreviations: OAB, overactive bladder

only a few study of flexible-dose fesoterodine in the Asian patients.

Therefore, in this study, we examined treatment satisfaction with flexible-dose fesoterodine in adult subjects with OAB who were dissatisfied with previous anticholinergic treatment in the Korean population.

MATERIALS AND METHODS

Study design

This prospective, multi-center, open-label, single-arm clinical study was conducted at seven different medical centers in Korea for 1 year. All seven centers are superior general hospitals under the college of medicine. Written informed consent was obtained from all subjects. The study was performed in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and the ethical principles of the Declaration of Helsinki.

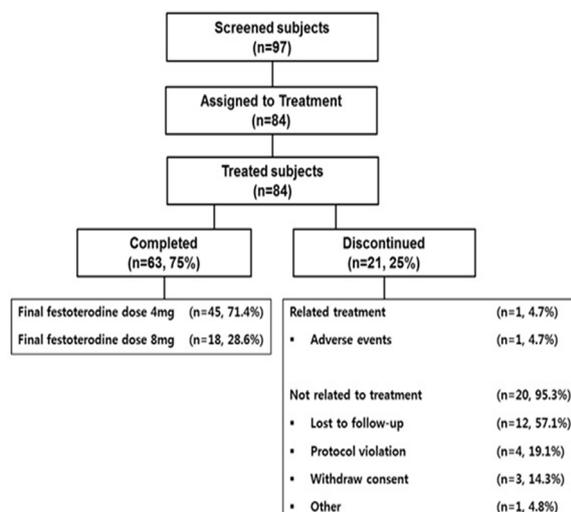
The duration of the study was 12 weeks except for a washout period of 2 weeks and a 2 weeks baseline period for screening. We recruited patients currently undergoing treatment for OAB or through an IRB-approved subject recruitment announcement. After 4 weeks with fesoterodine 4 mg daily, the dosage was either maintained at fesoterodine 4 mg daily or increased to 8 mg daily for the remaining 8 weeks of the study. Dose escalation was based on the subjects and physician assessments of efficacy and tolerability. If the symptom improvement was weak, the dose of fesoterodine was increased to 8mg, or if the side effects such as dry mouth were severe, 4mg of fesoterodine was maintained. Adherence was measured by pill counts.

Ethics

This study was approved by the Institutional Review Board of The Catholic University of Korea (HC10MI-MI0094).

Subjects

The study included men or women aged ≥ 18 years with OAB (mean micturition frequency of > 8 per 24 hours and mean number of urgency episodes > 3 per 24 hours in a 3-day voiding diary) for > 3 months who were “somewhat dissatisfied” or “very dissatisfied” in the five-point Likert scale with other anticholinergic treatments (propiverine, oxybutynin, trospium, and solifenacin) for at least 1 month. Subjects with the following conditions were excluded from the study: history of acute urinary retention requiring catheterization, neurogenic bladder, lower urinary tract surgery within 6 months, predominant stress urinary incontinence, significant pelvic organ prolapse, significant hepatic or renal function impairment, and any contraindications to



fesoterodine usage.

A sample size of 100 subjects was calculated to provide 10% level of margin for error and the 95% confidence interval for the percentage of treatment satisfaction rate at week 12. However, because the study was open label, the response to fesoterodine could be observed throughout the study. Therefore, the principal investigator decided to stop recruitment when obvious changes in subjects reporting treatment satisfaction were observed.

Outcome measurements

The primary end point of this study was patients' satisfaction after 12 weeks of fesoterodine treatment on a five-point Likert scale as follows: very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, and very dissatisfied. Secondary end points included changes from baseline to week 12 in the number of daytime micturitions, urgency incontinence episodes, urgency episodes with urgency scale (five-point urinary sensation scale as follows: no urgency, mild urgency, moderate urgency, severe urgency, and urge incontinence), and nocturnal micturitions in 24 hours from the baseline to the final assessment through a 3-day voiding diary. Safety assessments included adverse events.

Statistical methods

SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis. The data is presented as the mean ± standard deviation (SD). Comparative analysis of change of variables in the voiding diaries was performed with a two-sided paired t-test. A P-value of < .05 was considered statistically significant. Safety analysis included all subjects who received at least one dose of the study drug.

RESULTS

Subjects

Ninety-seven patients had been screened in 7 centers and 84 patients were enrolled and assigned to the treatment arm. The reasons for screening failure were that the inclusion criteria were not met or consent was withdrawn. Sixty-three patients completed the 12-week treatment period, while 21 did not. The reasons for discontinuation were adverse events, protocol violation, loss to follow-up, and consent withdrawal (**ure 1**).

Table 2. Change of parameters of the voiding diary per 24 hours from baseline to fesoterodine treatment at 4 weeks and 12 weeks

	Baseline mean \pm SD	4 weeks mean \pm SD	<i>p</i> -value (baseline vs. 4 weeks)	12 weeks mean \pm SD	<i>p</i> -value (baseline vs. 12 weeks)
No. of daytime micturitions	9.73 \pm 4.72	7.98 \pm 2.66	<0.001	7.76 \pm 2.86	0.001
No. of nocturnal micturitions	2.13 \pm 1.36	1.69 \pm 1.19	0.008	1.68 \pm 1.12	0.005
No. of urgency episodes	7.73 \pm 5.68	4.16 \pm 4.40	<0.001	3.71 \pm 4.09	< 0.001
No. of urgency urinary incontinence episodes	0.25 \pm 0.66	0.15 \pm 0.58	0.132	0.26 \pm 0.83	0.656

Data are presented as the mean \pm SD.

Abbreviations: SD, standard deviation

The average age of the patients was 59.1 \pm 13.3 years (range: 26 to 82 years) with the average age of female patients being 58.3 \pm 13.2 years (range: 26 to 82 years) and the average age of male patients being 64.4 \pm 10.3 years (range: 45 to 76 years). The mean duration for suffering from OAB was 42.6 \pm 37.8 months with 12 months or less in 15 patients (23.8%), 12 to 36 months in 25 patients (39.7%), and over 36 months in 23 patients (36.5%). The number of subjects that were “somewhat dissatisfied” with prior anticholinergics were 47 (74.6%) with 16 (25.4%) being “very dissatisfied” with prior anticholinergics (**Table 1**). Compliance on treatment after 12 weeks was 100% in 27 patients, 80-99% in 34 patients, and 60-79% in 2 patients.

Primary outcome variable

Sixty-three patients who conducted the evaluation of satisfaction and voiding diary on treatment for 12 weeks were available for efficacy evaluation. A final fesoterodine dose of 4 mg and 8 mg/day was used by 45 patients (71.4%) and 18 patients (28.6%), respectively. The satisfaction rate at 12 weeks of fesoterodine treatment was 69.9% (very satisfied at 19.1% and somewhat satisfied at 50.8%) and the dissatisfaction rate was at 14.2% (somewhat dissatisfied at 6.3% and very dissatisfied at 7.9%).

Secondary outcome variable

Mean changes in the number of daytime micturitions (9.73 \pm 4.72 vs. 7.76 \pm 2.86, *P* = .001), urgency episodes (7.73 \pm 5.68 vs. 3.71 \pm 4.09, *p* = 0.005), and nocturnal micturitions (2.13 \pm 1.36 vs. 1.68 \pm 1.12, *P* < .001) in 24 hours improved significantly with the flexible dose fesoterodine treatments. There was no statistically significant improvement in the number of instances of urgency urinary incontinence (**Table 2**).

Safety and tolerability

Eighty-four patients who participated in this clinical study who took fesoterodine at least 1 time and underwent safety evaluations were available for tolerability evaluation. Adverse events occurred in 22 patients (26.2%) at 12 weeks. Dry mouth was the most commonly reported adverse event and more commonly re-

ported at 12 weeks compared to 4 weeks. There were no serious adverse events (**Table 3**).

DISCUSSION

The main findings of this multicenter, open-label, single-arm clinical study were: (1) The satisfaction rate after 12 weeks of flexible-dose of fesoterodine treatment was approximately 70% with the dissatisfaction rate being around 14%. (2) Mean changes in the number of daytime micturitions, urgency episodes, and nocturnal micturitions in 24 hours improved significantly with flexible dose fesoterodine treatment. (3) Most of the adverse events that occurred were mild and none were severe.

These findings are consistent with the results of other previously published studies. The efficacy, safety, and tolerability of fixed dose fesoterodine (4 mg and 8 mg) for OAB were proven in two randomized clinical trials where the dose response effect of fesoterodine was defined.^(14,15) In superiority trial, fesoterodine 8 mg showed statistically significantly superior efficacy than fesoterodine 4 mg or placebo.⁽⁶⁾

Flexible-dose fesoterodine also significantly improved OAB symptoms and treatment satisfaction in several randomized, double-blind, placebo-controlled trials⁽¹⁶⁻¹⁹⁾ and open-label trials.^(10,11,20) Recent systematic review of data from these clinical trials showed that flexible-dose fesoterodine provided clinical benefit to patients with OAB because of its dose-response effects.⁽²¹⁾ These studies were designed to reflect clinical practice better in that the patients decided the dose escalation according to their clinical response rather than to a defined study protocol. In previous open label, flexible-dose trials of fesoterodine, 50 to 59% of subjects who received fesoterodine 4 mg requested dose escalation to 8 mg.^(10,11,20)

However, a final fesoterodine dose of 8 mg/day was used by only 18 patients (28.6%) in our study, while approximately 70% of subjects who requested fesoterodine 4 mg continuously or increase to 8 mg exhibited improvements in efficacy and tolerability as seen in other studies. Subjects who wanted to escalate their dose from fesoterodine 4 mg to 8 mg generally reported more severe baseline symptoms than subjects who wanted to continue the 4 mg dosage. The patients also exhibited lower improvements in efficacy and a higher incidence rate in adverse events during treatment with fesoterodine 4 mg. The patients' baseline symptoms in our study were better than other studies and the rate of adverse events was low during treatment. As a result, patients who wanted to increase their dose of fesoterodine were fewer in number.

There was no statistically significant improvement in

Table 3. Adverse events in response to fesoterodine treatment

Adverse events	4 weeks No. (%)	12 weeks No. (%)
Dry mouth	5 (5.9)	9 (10.7)
Dry eye	0 (0)	1 (1.2)
Constipation	1 (1.2)	1 (1.2)
Gastrointestinal discomfort	0 (0)	1 (1.2)
Voiding difficulty	2 (2.4)	2 (2.4)
Others (headache, leg edema, cystitis, gum bleeding, sore throat, diabetes, cervicalgia, cholangitis)	6 (7.1)	8 (9.5)

the number of instances of urgency urinary incontinence among the secondary outcome variables. While urgency urinary incontinence is considered a more notable symptom of OAB, continent OAB also has negative effects and decreases health-related quality of life. Coyne et al. reported that urinary urgency had a significant negative effect on health-related quality of life compared to incontinence urgency urinary incontinence in a national community survey using the National Overactive Bladder Evaluation Program.⁽²²⁾ Although urinary urgency can be quantifiable through counting urgency episodes in a voiding diary, this is insufficient to understand the patients' overall symptoms. Therefore, patient-reported outcome data should be investigated to measure the overall impact of treatment including adverse effects and tolerability.

The current study has several limitations. The main limitation of the study was the relatively small sample size compared to other similar studies. Therefore, these findings cannot be generalized to the entire Korean population. There was also a lack of male patients with most of subjects being women (87.3%). As a result, a study involving a larger sample including more men should be performed in the future. Second, this study was an open label study and did not include a placebo group. However, fesoterodine (4 mg and 8 mg) has been reported to be more efficacious for OAB symptoms than placebos in previous randomized placebo-controlled clinical trials.^(14,15) In addition, open-label studies are advantageous in that they reflect actual clinical practice and can determine an optimal balance between efficacy and tolerability. Third, we could not compare outcomes in subjects who received fesoterodine 4 mg for 12 weeks with subjects who escalated to the 8 mg dosage after 4 weeks. This is the limitation of an open-label, flexible dosing design because the baseline symptoms may vary between the two groups at the time of determination of dose escalation. Fourth, the satisfaction measurement was only dependent on the five-point Likert scale survey, not on the objective measurements. So the reliability of the responses of the patients about their satisfaction of the medication was considered low. This should be supplemented in future studies.

CONCLUSIONS

Patients with OAB who were dissatisfied with previous anticholinergic therapy had a high satisfaction rate and tolerated the flexible dose fesoterodine well. Therefore, this treatment represents an alternative treatment modality in patients with OAB who are dissatisfied with previous anticholinergic therapy in Korea. A study using a larger sample size including a number of male subjects should be performed in the future.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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