Clinical Medicine Reviews in Therapeutics

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REVIEW

Treatment of Overactive Bladder Symptoms with Extended Release Fesoterodine Fumarate

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Abstract: Fesoterodine extended-release (brand name Toviaz) is a new competitive muscarinic receptor antagonist labeled for the treatment of overactive bladder (OAB). Here we have undertaken a substantial update to a systematic review evaluating the effects of fesoterodine in the treatment of OAB. Our results indicate that fesoterodine was found to have significant improvements in the management of OAB symptoms compared with placebo. Post hoc analysis of these trials demonstrated significant improvements in health-related quality of life in patients with overactive bladder. Only one study included tolterodine, and direct comparisons between fesoterodine and tolterodine were not conducted. The most common treatment-emergent adverse effects associated with fesoterodine included dry mouth and constipation. In summary, fesoterodine appears to be effective and generally safe for the treatment of overactive bladder. Nonetheless, additional comparative trials are required to evaluate whether fesoterodine provides a substantial advantage over extended-release tolterodine.

Keywords: fesoterodine, overactive bladder, OAB, muscarinic receptor

Clinical Medicine Reviews in: Therapeutics 2010:2 103–113

This article is available from http://www.la-press.com.

Introduction

Overactive bladder (OAB) is a urological condition characterized by a set of symptoms: "frequency, urgency and nocturia, with or without urge incontinence in the absence of local pathology or metabolic factors that would account for these symptoms." OAB happens when the detrusor muscle of the bladder contracts more often than ordinary and at incorrect times. Instead of staying at rest, the detrustor contracts or squeezes when the bladder is filling with the urine. The International Continence Society (ICS) had defined OAB syndrome as urgency with or without urge incontinence, usually with frequency and nocturia. The basic diagnostic workup comprises symptoms assessment, targeted physical examination, urine analysis, post-void residual urine estimation which mostly allows to make a diagnosis and to find out which patients can be treated also by the non-specialist.[1] The bladder diary is an optimal diagnostic instrument with a lot of information, whereas urodynamics are invasive, expensive and somewhat remained undetermined.[2]

The prevalence of OAB increases with age and is more common in women than men. Prevalence estimates vary considerably among studies, ranging from 3% to 43%.[3] It was reported to be 12% to 17% in the US and Europe.[4–6] In addition, obesity is associated with symptoms of OAB, and the relationship between body mass index (BMI) and OAB with urge urinary incontinence appears stronger than that between BMI and OAB without urge urinary incontinence.[7]

While OAB is not a life-threatening condition, it can have a huge impact on quality of life. It can have an impact on even simply daily activities, such as work, travel, interpersonal activities, physical activity, sexual function, and sleep.[8] Treatment of OAB includes drugs, bladder training, pelvic floor exercises, electrical stimulation and lifestyle modification. Drugs for OAB include anticholinergic agents, antispasmodic medications, tricyclic antidepressants, and beta agonist may be initiated if the subjects do not respond to the above-mentioned regimens. With geographic differences, currently approved medical treatments are propiverine, propantheline, solifenacin, oxybutynin, tolterodine, flavoxate, darifenacin, imipramine, doxepin, terbutaline and trospium. Oxybutynin and tolterodine are antispasmodic medications and are the most commonly used and remain the first line treatment for patients with OAB probably due to easy access or time saving. However, pharmacotherapy improves OAB symptoms and quality of life but there are certain limitations in efficacy and tolerability.

Fesoterodine extended-release (brand name Toviaz) is a new competitive muscarinic receptor antagonist labeled for the treatment of overactive bladder. It was approved by the European Medicines Agency in April 2007 and was approved by the US Food and Drug Administration on October 2008 for the management of OAB symptoms. Since muscarinic receptors play a part in contractions of bladder smooth muscle and stimulation of salivary secretion, inhibition of these receptors in the bladder is presumed to be the mechanisms by which fesoterodine produces its effects. After oral administration, fesoterodine is rapidly converted to 5-hydroxymethyl tolterodine (5-HMT), which is responsible for the antimuscarinic activity of fesoteroidine. Unlike tolterodine, which is dependent on the cytochrome P450 (CYP) enzyme 2D6 in the liver for its initial conversion to 5-HMT, fesoterodine achieves this initial conversion and activation before entry into the liver via nonspecific, ubiquitous esterase. This is notable because CYP2D6 activity varies among individuals. Because fesoterodine does not require CYP2D6 metabolism for activation, it has the potential for less pharmacokinetic variability than tolterodine extended-release.

In this article, we undertake a substantial update to a systematic review assessing the effects of fesoterodine in the treatment of OAB. Medical literature on the use of fesoterodine was identified using MEDLINE, EMBASE and http://clinicaltrials.gov/, ww.emea.europa.eu/humandocs/PDFs/EPAR/toviaz/H-723-en6.pdf, additional references were identified from the reference lists of published articles.

Mechanism of Action

Binding of fesoterodine and several of its in vivo metabolites to human recombinant muscarinic acetylcholine receptors (M_1–M_5) was investigated in competition binding experiments. Fesoterodine acts as a pro-drug and is rapidly converted to its active metabolite 5-hydroxymethyltolterodine (5-HMT) [also known as SPM 7605] by non-specific esterase.[9]

Both agents are muscarinic receptor antagonists, but 5-HMT is more potent than the parent drug and is predominantly responsible for the antimuscarinic activity of fesoterodine.[10,11]

Fesoterodine and 5-HMT are non-selective muscarinic receptor antagonists. The presumed mechanism of action of antimuscarinic agents in OAB is the inhibition of muscarinic receptor on bladder smooth muscle and on the bladder tissue.[12,13] While all five subtypes of muscarinic receptors (M_1–M_5) have been identified in bladder tissue, M_2 and M_3 are most copious. In the detrusor muscle, M_2 outnumbers M_3 in a ratio of 3:1.[13] The M_3 receptor is considered most important in detrusor contraction, whereas the M_2 receptor may contribute to contraction by inhibition relaxation of bladder smooth muscle, among other possible mechanisms.[13]

Ney et al[14] in receptor binding studies using membrane preparations of Chinese hamster ovary cells expressing human muscarinic receptors, the mean binding affinities (Ki) of fesoterodine for muscarinic receptor subtypes M_1, M_2, M_3, M_4 and M_5 were 8.0, 7.7, 7.4, 7.3 and 7.5 nmol/L, respectively, and the corresponding Ki values for 5-HMT were 9.5, 9.2, 8.9, 8.7 and 9.2 nmol/L. They conducted an in vitro study of rat bladder strips, fesoterodine and 5-HMT (1 mmol/L to 1 mol/L) demonstrated competitive antagonism, as evidenced by a rightward shift of the concentration-response curve for carbachol-induced contractions without a significant depression of the maximum.[14] In addition, they also found contractions of rat bladder strips induced by electrical field stimulation were inhibited in a dose-dependent manner by fesoterodine and 5-HMT, with similar potency to that demonstrated with oxybutynin and atropine.[14]

Fesoterodine 0.1 mmol/L and 5-HMT 0.1 mmol/L caused 46% and 45% inhibition of contractions compared with 34% and 40% with oxybutynin 0.1 mmol/L and atropine 0.1 mmol/L.[14] Low doses of intravenous fesoterodine and 5-HMT (0.01 mg/kg) caused significant ($P < 0.05$) increases from baseline in healthy rat bladder capacity and micturition intervals, and significantly ($P < 0.01$) reduced micturition pressure compared with baseline.[13] Higher doses (0.1 and 1.0 mg/kg) did not further decrease micturition pressure, but bladder capacity and micturition intervals were unchanged at 0.1 mg/kg and decreased ($P < 0.05$) at 1.0 mg/kg. Residual volume was not significantly affected by any of the three fesoterodine and 5-HMT doses.[14]

Malhotra et al[15] studied the effect of oral fesoterodine on cardiac electrical activity and they found fesoterodine did not affect myocardial repolarization compared with placebo.[15] ECGs of 256 healthy volunteers were obtained at 12 time-points on day 0 (baseline) and on days 1 and 3 after receiving once-daily fesoterodine 4 or 28 mg, moxifloxacin (control) or placebo for 3 days in a double-blind, parallel-group study. Corrected QT interval changes from baseline with both fesoterodine dosages were not significantly different from those with placebo.[15]

Metabolism

In vitro, fesoterodine is extensively metabolized by non-cytochrome P450 activity to the major metabolite SPM 7605 (5-HMT) (human, rabbit > mouse > dog >> rat). Further metabolism takes place via CYP2D6 to the carboxy metabolite SPM 5509 (major) or via CYP3A4 to the N-desisopropyl metabolite SPM 7789 (minor). Both SPM 5509 and SPM 7789 are then further metabolized to SPM 7790.[11]

In vivo, in all animal species (and humans), the major biotransformation pathways involved rapid hydrolysis that leads to the formation of SPM 7605 followed by oxidation and N-dealkylation (mediated both by CYP activity). In these species, fesoterodine cannot be detected in plasma and SPM 7605 can be regarded both as major metabolite and active principle of fesoterodine. No gender differences have been observed except in the rat. The dog does not hydrolyze fesoterodine to the same extent as observed in the other species, thus fesoterodine can be detected in plasma of the dog together with the other metabolites. No or low inhibitory interactions with CYP1A2, 2C9, 2C19, 2D6 and 3A4 were detectable for fesoterodine.[11]

Fesoterodine and/or its metabolites are rapidly excreted with the majority of the dose recovered within 48 hours. In the dog, the majority of radioactivity (60%–67%) was excreted in urine. Both urinary and fecal elimination are relevant in the mouse. In the rat, the largest portion of radioactivity was recovered

in feces. In humans, about 70% of an oral dose of fesoterodine is recovered in urine.[11]

Pharmacokinetic Profile

We summarizes pharmacokinetic profile data from the manufacturer's prescribing information,[10,11] and a single-centre, open-label, randomized, 4-way cross-over study in a total of 24 healthy male volunteers following single oral doses of 4, 8, or 12 mg fesoterodine while fasting or 8 mg dose administered after a standard high-fat and high calorie breakfast.[16]

- After intake, fesoterodine is rapidly and extensively hydrolyzed by nonspecific plasma esterase to form the active metabolite 5-HMT.[10,11]
- After intake single or multiple oral daily doses (4–28 mg) of fesoterodine, 5-HMT demonstrated dose-proportional pharmacokinetics.[10,11] The plasma protein binding of 5-HMT is low (≒50%). The time to (t_{max}) maximum plasma concentration (C_{max}) of 5-HMT is about 5 hours, and multiple doses do not result in accumulation. In addition, metabolism of 5-HMT is primarily via the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4.[10,11] In CYP2D6 poor metabolizers, the 5-HMT C_{max} was increased by about 1.7-fold compared with extensive metabolizers. After a single oral dose of fesoterodine 4 mg, the 5-HMT C_{max} was 1.89 ng/mL in extensive metabolizers and 3.45 ng/mL in poor metabolizers. After a single dose of fesoterodine 8 mg, the corresponding C_{max} values were 3.98 and 6.90 ng/mL.[10,11]
- In CYP2D6 poor metabolizers, the 5-HMT AUC0-t (Area Under the Concentration-time Curve From Time Zero to Time of Last Measurable Concentration) was increased 2-fold compared with extensive metabolizers.[10,11] After a single oral dose of fesoterodine 4 mg, the 5-HMT AUC was 21.2 ng~h/mL in extensive metabolizers and 40.5 ng~h/mL in poor metabolizers. After a single dose of fesoterodine 8 mg, the corresponding AUC values were 45.3 and 88.7 ng~h/mL.[10] The t_{max} was unchanged in poor metabolizers compared with extensive metabolizers.[10,11]
- After intake of fesoterodine, about 70% of the dose is excreted by kidney as metabolites, and a small amount is excreted in the faeces (7%).[10,11] The terminal elimination half-life (t1/2β) of 5-HMT after oral administration is not affected by CYP2D6 status.[10] In poor and extensive metabolizers, the t1/2β was 7.31 hours after a single dose of fesoterodine 4 mg and 8.59 hours after a single dose of fesoterodine 8 mg. In addition, the pharmacokinetic profile of fesoterodine is not altered to a clinically significant extent by sex or age; the pharmacokinetics of the drug has not been assessed in children.[10,11] Furthermore, there were no apparent differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy volunteers.[10]
- In patients with moderate (Child-Pugh B) hepatic impairment, the total exposure to 5-HMT was about 2-fold higher than that of healthy volunteers.[10] No dosage adjustment is recommended in patients with mild to moderate hepatic impairment, however, fesoterodine is not recommended in patients with severe (Child-Pugh C) hepatic impairment.[10] Exposure to 5-HMT is increased by up to 1.8-fold in patients with mild to moderate renal impairment (creatinine clearance [Ccr] of 30–80 mL/min) and by 2.3-fold in patients with severe renal impairment (Ccr $<$ 30 mL/min).[10] No dosage adjustment is required in patients with mild to moderate impairment, but doses of fesoterodine above 4 mg are not recommended in patients with severe renal impairment. In addition, exposure to 5-HMT is increased when fesoterodine is combined with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and clarithromycin, in CYP2D6 poor and extensive metabolizers. As a result, doses of fesoterodine above 4 mg are not recommended in combination with these agents.[10]
- Plasma concentrations of 5-HMT increased proportionally with fesoterodine dose. Mean C_{max} were 2.3 ng/mL (4 mg fesoterodine), 4.8 ng/mL (8 mg fesoterodine), and 7.3 ng/mL (12 mg fesoterodine) in the fasted state. Statistical analysis of dose normalized C_{max} and AUC values concluded linear pharmacokinetics of 5-HMT following the administration of 4, 8, and 12 mg fesoterodine in the fasted state.[16] Interestingly, mean C_{max} and mean AUC0-t significantly increased approximately 1.30- and 1.18-fold, respectively, after a standard high-fat and high-calorie meal. The 90% confidence intervals for the fed versus fasted treatment ratios were 123% to 141% and 110% to 127% for C_{max} and AUC respectively. The confidence interval for C_{max} ratio

was contained entirely with in the pre-specified acceptance range of 70% to 143%; however, the range for the AUC ratios was just outside the upper limit of the acceptance range of 80% to 125%. Mean t_{max} was not affected.[16]

- Considering tolterodine and 5-HMT are known to be metabolized by CYP2D6,[17] an assessment of the effect of CYP2D6 status on the pharmacokinetics of 5-HMT was conducted. 16 of the 24 subjects in this study were enrolled as extensive metabolizers (EM) and 8 as poor metabolizers (PM).[16] When separately analyzed EM and PM regarding the pharmacokinetics of 5-HMT following administration of fesoterodine, significantly increased mean C_{max} levels in PM compared with EM (approximately 2-fold) were found; Accordingly, mean AUC0-t was increased in PM compared with EM (approximately 2-fold). These results were not due to differences in the baseline characteristics between PM and EM groups. In contrast, mean t_{max} and mean t1/2 did not differ between PM and EM. Fesoterodine exhibits flip-flop PK in that the terminal half-life of 5-HMT reflects the extended-release rate from the fesoterodine formulation. Due to flip-flop kinetics, modest changes in metabolic clearance, as demonstrated on the basis of CYP2D6 metabolizer status, do not affect the terminal half life of 5-HMT. As a result, for 5-HMT the time to reach steady state and the accumulation ratio, each determined by the half life, are likewise not expected to differ between CYP2D6 EMs and PMs. Additionally, the influence of a standard high-fat and high-calorie meal before fesoterodine administration was similar in both groups. The mean excretion of 5-HMT in urine was significantly increased in PM compared with EM (approximately 2-fold). Moreover, consistent with the slightly higher AUC of 5-HMT in the fed state, there was a small but statistically significant increase in the urinary excretion of 5-HMT following administration of fesoterodine under these conditions. In contrast, the mean renal clearance was affected neither by the CYP2D6 nor the fed status.[16]

Clinical Studies

An extensive computer-based literature search as well as a search through reference sections of obtained articles was performed to retrieve randomized controlled trials on men and women with a diagnosis of OAB, providing one arm of the study used fesoterodine. The search was done using the http://clinicaltrials.gov/, the US national Institute of Health maintained database for most clinical trials conducted in the United States and around the world, for all federally and privately supposed clinical trials. We included studies published through November 2009.

During the search process all abstracted of the identified publications were screened independently by two authors and studies were selected if they met all of the following inclusion criteria: (1) the study was a randomized controlled trials, (2) included men and women with OAB symptoms of urge urinary incontinence, urgency and urinary frequency, (3) investigated the effectiveness of fesoterodine, (4) written in English, (5) not a review or containing a repeated study published in a previous article (i.e. in the later case, the effect size was extracted from only one article). Summaries of the clinical trials to evaluate the safety and efficacy of fixed dosage fesoterodine included in this review are presented in Table 1. Using ClinicalTrials.gov, a total of 29 randomized clinical trials were retrieved; of these 17 studies were completed, 11 studies were recruiting, and 1 studies were not yet recruiting. Among the 17 completed clinical trials, 3 of them have results available. Next, the full articles were obtained for the selected clinical trials. Some studies were associated with more than one publication, but we have referenced only the principal publication. In case of any doubt or disagreement between the reviewers, the publication was included.[18]

Table 2 summarizes the inclusion and exclusion criteria for the included clinical trials. 2 of those trials were double-blinded and randomized, whereas the remaining one was open-label and non-randomized. Among those 3 trials, 2 of them were double-blind, whereas one was open level. Study lengths are always 52 weeks. The numbers of patients in trials ranged from 512 to 1712. The ages eligible for study is 18 years and older. The subjected included men and women with OAB symptoms of urge urinary incontinence, urgency and urinary frequency.

The primary outcomes of interest were the mean change in the number of urge urinary incontinence episodes per day and the mean change in the number of

Table 1. Review of fixed dosage fesoterodine ER clinical studies.

Interventions	Authors	Study start date	Study end date	Sample size	Trial length	Blinding/ randomization
Arm 1: Fesoterodine 4 mg once daily for 2 weeks, then either 4 mg or 8 mg tablets once daily for 10 weeks Arm 2: Placebo	Chapple[19]	Aug 2007	Mar 2008	896	12	Double-blinded randomized
Arm 1: Fesoterodine 4 mg once daily for 4 weeks; then, daily dosage was maintained at 4 mg or increased to 8 mg Arm 2: Placebo	Nitti[13,22]	Jan 2007	Oct 2007	516	12	Open label non-randomized
Arm 1: 4 mg once daily for 1 week followed by a forced dose-escalation to 8 mg once daily for 11 weeks Arm 2: Placebo once daily for 12 weeks Arm 3: Tolterodine tartrate 4 mg once daily for 12 weeks	Chapple[21]	Apr 2007	Jul 2008	1712	12	Double-blinded randomized

micturition per day. An important secondary outcome of interest was the mean change in the voided volume per micturition. Methodological quality was evaluated by considering the adequacy of random allocation and concealment description of dropouts and withdrawals, analysis of intention to treat, and blinding during treatment and at outcome assessment. In those trials, the primary and secondary outcomes of interest was assessed by having patients complete a bladder diary, in which they recorded the number of micturition and urgency urinary incontinence (UUI) episodes over 24 hours, severity of urinary urgency, and voided volume per micturition.

Safety

The safety of fesoterodine was established in 3 studies.[13,18,19] In general, adverse effects did not significantly differ between fesoterodine and placebo groups. The most frequently reported adverse event in patients treated with fesoterodine was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day and in those taking 4 mg/day, as compared to placebo. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment. The second most commonly reported adverse event was constipation. Treatment-emergent adverse reactions that had a high incidence with fesoterodine compared with placebo were dry mouth, urinary tract infection, upper respiratory tract infection, constipation, and nausea.[13,18] There were no clinically relevant changes from baseline in vital signs.[13,18]

In details, we summarizes the tolerability of oral fesoterodine 4 and 8 mg once daily in patients with OAB as reported in two large, phase III studies.[13,19] Fesoterodine 4 and 8 mg once daily was generally well tolerated and the number of patients who discontinued therapy due to adverse events was low in both trials.[13,19] For example, in the US trial, 4%, 6% and 9% of patients receiving placebo, fesoterodine 4 or 8 mg once daily, respectively, discontinued therapy due to an adverse event,[13] and in the European study, the corresponding incidence of patient withdrawals was 2%, 3% and 5% (and 3% with tolterodine extended release (ER) 4 mg once daily).[19] The most frequent adverse event in all treatment groups of both studies was dry mouth, which was generally mild to moderate in severity.[13,19] In the US trial, dry mouth was reported by 7%, 16% and 36% of patients receiving placebo or fesoterodine 4 or 8 mg once daily, and this event led to treatment discontinuation in 1% of patients receiving fesotero-

Table 2. Summaries of inclusion and exclusion criteria for included trials.

Authors	Inclusion criteria	Exclusion criteria
Chapple[19]	Overactive bladder symptoms for greater than or equal to 3 months. Mean urinary frequency of greater than or equal to 8 micturitions per 24 hours in bladder diary. Mean number of Urgency episodes greater than or equal to 3 per 24 hours in bladder diary.	Contraindication to fesoterodine (antimuscarinics). Known etiology of OAB (e.g. neurogenic, local urinary tract pathology). Previous history of acute urinary retention requiring catheterization or severe voiding difficulties in the judgment of the investigator, prior to baseline. Unable to follow the study procedures, including completion of self-administered bladder diary and patient reported outcome questionnaires.
Nitti[13,22]	OAB patients who present with OAB symptoms (≥8 micturitions and ≥3 urgency episodes per 24 h documented in the baseline bladder diary). OAB patients dissatisfied with their prior therapy with tolterodine.	Patients with any contraindication to fesoterodine usage, e.g. urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or known hypersensitivity to the drug or its ingredients. Patients with significant hepatic and renal disease or other significant unstable diseases. OAB symptoms caused by neurological conditions, known pathologies of urinary tract, etc.
Chapple[21]	Adult male and female patients (> = 18 years old and overactive bladder (OAB) patients who present with OAB symptoms, including urinary frequency > = 8 per day and urgency urinary incontinence > = 1 per day.	Patients with conditions that would contraindicate for fesoterodine use, e.g. hypersensitivity to the active substance (fesoterodine) or to peanut or soya or any of the excipients, urinary retention, and gastric retention. Patients with significant hepatic and renal disease or other significant unstable diseases. OAB symptoms caused by neurological conditions, known pathologies of urinary tract, etc.

dine 4 mg and 2% of patients receiving fesoterodine 8 mg.[12] Other adverse events commonly associated with treatment included constipation, headache and dry eyes.[13,19]

Urinary retention requiring catheterization occurred in one patient in the European trial, but mild to moderate urinary retention occurred in ten patients in the US study (none required catheterization), four (1%) in the fesoterodine 4 mg once-daily group and six (2%) in the fesoterodine 8 mg once-daily group; one male patient receiving placebo developed severe urinary retention.[13] Overall, fesoterodine treatment was not associated with any clinically relevant changes in vital signs, such as heart rate or blood pressure, or in laboratory parameters or ECG recordings.[13,19] Mean changes in heart rate were similar in fesoterodine treatment groups in both studies.[13,19] In the European study, the mean changes from baseline in heart rate with placebo, fesoterodine 4 or 8 mg once daily, or tolterodine ER 4 mg once daily were 0.8, 3.3, 3.9 and 2.8 beats per minute, respectively.[13,19]

Wyndaele et al[20] reported dry mouth (23%) and constipation (5%) were the most frequently reported adverse events; most of these were mild or moderate in severity. Urinary retention requiring catheterization was reported by one woman receiving fesoterodine 8 mg who withdrew from the study. Two women receiving the 4-mg dose were reported to have urinary retention not requiring catheterization; one withdrew from the study. No cases of urinary retention occurred in men. The overall withdrawal rate was 10% and the rate of withdrawal due to treatment-emergent adverse events regardless of causality was 7%. There were no deaths during the study; nine subjects (<2%) reported serious adverse events, none of which was deemed to be treatment related.

In addition, based on the animal studies (i.e. via the oral and i.v. routes of administration in the mouse and rat) investigated by Pfizer Labs including toxicology, genotoxicity, carcinogenicity, reproduction toxicity, antigenicity, biocompatibility, immunotoxicity and phototoxicity revealed satisfactory.[11]

Efficacy

Trials of fesoterodine supplied data for the meta-analysis. Trials were excluded from the meta-analysis because they lacked adequate frequency data, did not provide pre-crossover statistics, or because there were inadequate numbers of fair- or good-quality trials to combine.

The efficacy of oral once-daily fesoterodine 4 or 8 mg in patients with OAB has been evaluated in three large, randomized, double-blind, placebo-controlled, multicentre, phase III trials.[13,19,20] Results of phase II, placebo-controlled studies had previously demonstrated the efficacy of fesoterodine 4, 8 or 12 mg/day in patients with OAB.[21,22]

In the phase III studies, one of which was performed in the US[13] and the other predominantly in Europe,[19] eligible patients were aged ≧18 years and had been experiencing non-neurogenic OAB with or without urge incontinence for ≧6 months. The frequency of micturition was required to be at least eight voids in 24 hours and patients were also required to experience urgency episodes at least six times or urge incontinence at least three times on 3 days during the run-in period.[13,19] Most patients were female (~78%) and the mean age was similar in both studies (59[13] and 57[19] years). The mean time from diagnosis of OAB was 8–10 years, and approximately half of the patients in the US study[13] and about 40% of patients in the European study[19] had received previous drug therapy for their condition.

Both trials incorporated a 2-week placebo run-in period followed by 12 weeks' treatment, after which patients had the option to continue in a long-term, open-label study or complete a 2-week safety follow up.[13,19] During the treatment phase, patients received placebo (n = 271[13] and 283[19]), fesoterodine 4 mg once daily (n = 282[13] and 272[19]) or fesoterodine 8 mg once daily (n = 279[13] and 287[19]). The European study included a fourth treatment arm of tolterodine ER 4 mg once daily (n = 290) as an active control (i.e. it was not designed to compare the efficacy of fesoterodine with tolterodine).[19] The primary efficacy endpoint was the change from baseline to the end of treatment in micturition frequency in 24 hours.[13,19] Efficacy was assessed by a 3-day diary completed by the patient during the run-in period and prior to subsequent visits. Co-primary variables included the change in the number of episodes of urge incontinence in 24 hours compared with baseline, and patient assessment of overall treatment response, which was derived from a 4-category treatment benefit scale (from 1 = greatly improved to 4 = worsened condition); the response was 'yes' if the answer was 1 or 2, and 'no' if the answer was 3 or 4.[13,19] The impact of fesoterodine on health-related quality of life (HR-QOL) was evaluated in a post hoc analysis of pooled data from both of the phase III trials (n = 1903).[13,19] Evaluations were based on the King's Health Questionnaire (KHQ; assesses nine domains including severity/coping, emotions, role limitations, physical limitations, social limitations, sleep/energy, personal relationship, incontinence impact and general health perception), the International Consultation on Incontinence Questionnaire short form (ICIQ-SF; assesses the effects of urinary frequency and urine leakage on daily life), a 6-point Likert scale (0 = no problem to 5 = very severe problems) and the self-reported 4-point treatment benefit scale.[21,22]

In Wyndaele's series[20] they reported statistically significant improvements from baseline to week 12 were observed in mean number of micturition, urgency urinary incontinence (UUI) episodes and urgency episodes ($P < 0.0001$ for all comparisons). Statistically significant improvements in nocturnal micturition, severe urgency episodes and frequency-urgency sum were also observed at week 12 ($P < 0.0001$ for all comparisons). The corresponding median percentage change from baseline to week 12 was 22% for micturition frequency, 100% for UUI episodes, 57% for urgency episodes, 31% for nocturnal micturition and 94% for severe urgency episodes.

Wyndaele et al reported.[20] At 12 weeks, 80% of subjects who responded to the Treatment Satisfaction Question reported being satisfied with fesoterodine treatment, with 38% of subjects being 'very satisfied'. Mean Patient Perception of Bladder Condition (PPBC) questionnaire scores improved significantly from 4.9 at baseline to 3.1 at week 12 ($P < 0.0001$). By week 12, 83% of subjects reported improvement on the PPBC, with 59% of subjects

reporting improvement ≥2 points. The proportion of subjects reporting severe or many severe problems was reduced from 68% at baseline to 12% after 12 weeks, whereas the proportion reporting no problems, very minor problems or minor problems was increased from zero at baseline to 63% at 12 weeks. Mean Urgency Perception Scale (UPS) scores improved significantly from 1.8 at baseline to 2.4 at week 12 ($P < 0.0001$). UPS scores improved in 49% of subjects, deteriorated (post hoc analysis) in 2%, and were unchanged in the remaining subjects. The proportion of subjects who reported that they were usually urgent incontinence was reduced from 25% at baseline to 6% after 12 weeks. The proportion of subjects who reported being able to suppress urgency was increased from 6.8% at baseline to 41% after 12 weeks. The mean change in Overactive Bladder Questionnaire (OAB-q) symptom bother score (29-point improvement) from baseline to week 12 was statistically significant ($P < 0.0001$). Mean changes in total health-related quality of life (HRQL) (26-point improvement) and all four HRQL domain (Concern, 29-point improvement; Coping, 31-point improvement; Sleep, 25-point improvement; Social Interaction, 17-point improvement) scores were also statistically significant at 12 weeks, compared with baseline ($P < 0.0001$). The improvements for all scales and domains were well above the minimally important difference of 10 points, indicating that these changes were clinically relevant.[23]

Patient Preference

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 mechanism of antimuscarinic action, the relative contribution of typical adverse events for any antimuscarinic agent were most likely due to different muscarinic receptor subtypes.[24]

Khullar et al reported the incidence of dry mouth increased from 19% (fesoterodine 4 mg) to 35% (fesoterodine 8 mg; placebo [PBO], 7%) with most cases being mild to moderate in nature.[25] This incidence rate is somewhat higher than that reported for solifenacin (5 mg, 11%; 10 mg, 28%; PBO, 4%)[26] and is lower than that reported for oxybutynin (5 mg, 56%; 10 mg, 68%; 15 mg, 70%)[27] and darifenacin (7.5 mg, 23%; 15 mg, 40%; PBO, 8%).[28] Nitti et al reported dry mouth was the most commonly adverse event in 4 and 8 mg fesoterodine of adverse events leading to discontinuation dry month was given as reason by 1% of subjects on 4 mg fesoterodine and by 1.8% on 8 mg fesoterodine.[13]

Comparing 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),[27] 5% and 13% with solifenacin (5 and 10 mg, respectively)[26] and 16% and 25% with darifenacin (7.5 and 15 mg, respectively).[28] The low incidence of constipation with fesoterodine may be attributed to its nonselective receptor binding profile. Nitti et al reported constipation led to discontinuation in less than 1% of subjects on 8 mg fesoterodine. Urinary retention and increased post-void residual led to discontinuation in 1% of the subjects in the 4 mg fesoterodine group and in the 8 mg fesoterodine group.[13]

Place in Therapy

Fesoterodine is a novel antimuscarinic agent and unlike the other antimuscarinics, which have shown rare dose-response relationship and dose related increases in adverse events, such as dry month, constipation and blurred vision. Phase I studies have shown that fesoterodine is associated with a dose-dependent pharmacokinetic profile and relatively low pharmacokinetic variability.[9,29]

Fesoterodine significantly improved OAB symptoms as early as 2 weeks after initiation of treatment. Fesoterodine 8 mg was significantly more efficacious than the 4 mg dose in improving UUI episodes, urgency episodes, bladder capacity, continent days, and treatment response.[25] In the study, treatment with 4 or 8 mg fesoterodine demonstrated statistically significant and clinically relevant improvements compared with placebo for OAB symptoms. Fesoterodine 8 mg was significantly more efficacious than the 4-mg dose in improving UUI episodes, urgency episodes, bladder capacity (assessed as maximum voided volume [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 among the 15-mg dose and the 2 lower doses (5 and 10 mg) for reduction of UUI episodes and MVV per micturition.[27] Dose separation has not been demonstrated for efficacy outcomes with darifenacin,[30] solifenacin,[31] or tolterodine.[32,33] The reasons for the fesoterodine dose response may lie in its pharmacokinetic and pharmacologic profile.

Regarding the cost for 30 days' treatment with the lowest recommended adult dosage, according to March 2009 data from retail pharmacies nationwide available from Wolters Kluwer Health: $138.60 for darifenacin hydrobromide, 139.50 for fesoterodine, 120.90 for oxybutynin chloride, 136.80 for solifenacin succinate, 137.10 for tolterodine tartrate, and 129.90 for trospium chloride. The financial burden for patient receiving fesoterodine is among the average.

Some opinions did not favor and they conclude fesoterodine (Toviaz) offers no clear advantage over the 5 antimuscarinic drugs previously approved for overactive bladder. Its maximum approved dose (8 mg) has been more effective than the maximum approved dose of tolterodine (4 mg), but also causes more dry mouth,[34] in addition. Tzofes et al concluded the efficacy and safety of fesoterodine in overactive bladder treatment seem to be at least similar to that of tolterodine.[35]

Conclusions

We have undertaken a substantial update to a systematic review assessing the effects of fesoterodine in the treatment of OAB. Our results indicate that fesoterodine was found to have significant improvements in the management of OAB symptoms compard with placebo. Post hoc analysis of these trials demonstrated significant improvements in health-related quality of life in patients with overactive bladder. Only one study included tolterodine, and direct comparisons between fesoterodine and tolterodine were not conducted. The most common treatment-emergent adverse effects associated with fesoterodine included dry mouth and constipation. In summary, fesoterodine appears to be effective and generally safe for the treatment of overactive bladder. Nonetheless, additional comparative trials are required to evaluate whether fesoterodine provides a substantial advantage over extended-release tolterodine.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest.

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