Fesoterodine: A New Agent for Treating Overactive Bladder

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Abstract

Objective: To review the efficacy and safety of fesoterodine, a new antimuscarinic for treating overactive bladder (OAB) symptoms.

Methods: Review of efficacy and safety data from the pivotal phase 3 trials of fesoterodine for the treatment of OAB. Although there were a number of additional end points, they were not included in the US prescribing information for fesoterodine and thus are not included in this article.

Results: OAB is a chronic condition affecting both men and women. The principal symptom is urgency, with or without urgency incontinence, with some patients experiencing increased daytime frequency and nocturia. In two 12-week, randomized, double-blind, phase 3 trials, fesoterodine 4 and 8 mg administered once daily were significantly better than placebo in alleviating OAB symptoms, as determined by changes in bladder diary variables. Both doses of fesoterodine were well tolerated.

Conclusions: Fesoterodine is an efficacious, well-tolerated treatment for OAB.

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Overactive bladder (OAB), a common condition affecting 11% to 17% of men and women,[1,2] is a syndrome with symptoms defined by the International Continence Society as urgency, with or without urgency incontinence, and usually with increased daytime frequency and nocturia.[3] Patients with OAB have a sudden, compelling need to urinate that cannot be easily deferred (urgency) and feel they need to urinate too many times throughout the day (frequency).[4] Patients may also be awakened during the night by the need to pass urine (nocturia).[4]

Despite its high prevalence, OAB is underdiagnosed and undertreated,[5] and some patients may not seek medical help for years after OAB onset because they consider the symptoms a normal part of aging.[5] This is unfortunate because of the substantial impact OAB has on health-related quality of life.[2,6]

OAB symptoms can be treated using nonpharmacologic measures, such as behavioral interventions and lifestyle modification, or drug therapy, with antimuscarinics being the principal pharmacologic treatment for OAB. Despite the effectiveness of these agents for OAB, most patients discontinue antimuscarinics within 6 to 12 months after inititation.[7]

FESOTERODINE

Fesoterodine, a new antimuscarinic agent for treating OAB, works by blocking muscarinic receptors. These receptors are found on the detrusor muscle, which contracts when a person urinates and relaxes when the bladder fills with urine.[8] Muscarinic receptors are also found on urothelial cells in the bladder,[8] where they may mediate activity of afferent nerves, which are involved in bladder control. In patients with OAB, normal bladder function is disrupted, resulting in an "overactive" bladder.

The parent drug fesoterodine is not a potent antimuscarinic; its antimuscarinic activity results from the active metabolite 5-hydroxymethyl tolterodine (5-HMT), a balanced muscarinic receptor blocker without selectivity for any particular muscarinic receptor subtype.[9] 5-HMT is formed when fesoterodine is hydrolyzed by nonspecific esterases. This conversion is rapid and extensive, such that no fesoterodine is detectable in blood after oral administration.[10] 5-HMT is metabolized in the liver to its carboxy, carboxy-N-desiso-

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propyl, and N-desisopropyl metabolites via 2 major pathways involving members of the cytochrome P450 (CYP) system, CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. After oral administration of fesoterodine, approximately 70% of the administered dose is recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) is recovered in feces.

EFFICACY AND SAFETY

The efficacy and safety of fesoterodine have been demonstrated in two 12-week, randomized, double-blind, phase 3 trials, one conducted at 150 sites in 19 countries and the other at 83 sites in the United States.[11,12] In both trials, efficacy was assessed by having patients complete a bladder diary, in which they recorded the number of micturitions and urgency urinary incontinence (UUI) episodes over 24 hours, severity of urinary urgency, and voided volume per micturition.

In the international trial,[11] 1132 patients received study medication, either fesoterodine 4 or 8 mg once daily, placebo, or another oral antimuscarinic (active control) for 12 weeks. Compared with placebo, both fesoterodine doses significantly decreased the total number of micturitions, urgency episodes, and UUI episodes over 24 hours and increased the mean voided volume (P <.05). In the US trial,[12] 832 patients were treated with fesoterodine 4 or 8 mg once daily or placebo. Both fesoterodine doses were significantly better than placebo in decreasing the total number of micturitions, urgency episodes, and UUI episodes over 24 hours (P <.05), and the fesoterodine 8-mg dose significantly increased the mean voided volume per micturition compared with placebo (P <.001).[12]

Dry mouth was the most common adverse event reported with fesoterodine in both trials and occurred more often with the higher dose. In the international trial, dry mouth occurred in 22% of patients taking fesoterodine 4 mg and in 34% of those given fesoterodine 8 mg versus 7% of patients given placebo; in the US trial, the percentages were 16% and 36%, respectively, versus 7% for placebo. For most patients in both trials, dry mouth was mild or moderate, with no more than 2% of patients withdrawing from any fesoterodine group because of this adverse event. In both trials, constipation was reported by 3% to 8% of patients in the fesoterodine groups and by 1% to 3% of patients in the placebo groups. Other less common adverse events reported in more than 2% of patients treated with fesoterodine 4 or 8 mg included urinary tract infection, headache, and dry eye. Central nervous system adverse events with fesoterodine occurred at the same rate as placebo in both trials.

In a double-blind, placebo-controlled study to assess the effect of fesoterodine on corrected QT interval, healthy volunteers were given therapeutic (4 mg) or supratherapeutic (28 mg) doses of fesoterodine or moxifloxacin 400 mg as an active control.[13] Electrocardiographic results over 3 days of once-daily treatment indicated that fesoterodine does not affect cardiac repolarization.

Fesoterodine is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients with known hypersensitivity to the drug or its ingredients. In addition, fesoterodine should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, and significantly reduced hepatic or renal function. Fesoterodine is not recommended for use in patients with severe hepatic impairment.

Additional analyses and phase 3b/4 studies, including a flexible-dose study, have been conducted since the phase 3 trials were completed and have been published in peer-reviewed journals.[14-17]

CONCLUSIONS

OAB is a common condition affecting both men and women, with prevalence increasing with age. Persons with OAB experience urgency and sometimes UUI, necessitating frequent visits to the restroom throughout the day and often at night. To avoid the embarrassment of "accidents" before reaching a restroom, OAB patients may curtail their activities, preferring to remain at home or ensuring that a restroom is available when they go out.

Although nonpharmacologic therapies may help alleviate OAB symptoms, antimuscarinic drugs provide symptom relief for many patients. Fesoterodine

is a new antimuscarinic agent shown to be efficacious and well tolerated for treating OAB symptoms, including UUI. Fesoterodine is administered once daily and is available in 2 doses, which allows for flexibility in dosing to meet the individual needs of the patient.

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