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FESOTERODINE IS AN EFFECTIVE ANTIMUSCARINIC FOR PATIENTS WITH OVERACTIVE BLADDER (OAB): RESULTS OF A PHASE 2 TRIAL.

Hypothesis / aims of study
Fesoterodine fumarate is a potent new antimuscarinic that is immediately de-esterified to its active metabolite without requiring the classical pathway of hepatic metabolism through cytochrome P450 for its pharmacologic activity.
The objective of this study was to investigate efficacy and safety of sustained release fesoterodine in subjects with OAB and determine the dose-response relationship.

Study design, materials and methods
In a multicenter double-blind, randomized, placebo-controlled trial, following a 1-week placebo run-in, eligible OAB male and female patients with or without baseline urodynamic evidence of detrusor overactivity were randomized to receive placebo or 4, 8, or 12 mg of fesoterodine once daily for 8 weeks. Subjects were required to have ≥ 8 micturitions/24 hours and ≥ 2 urge incontinence episodes/week during the run-in week. Assessments included numbers of micturitions/24 hours (primary efficacy), urge incontinence episodes/week, and voided volume per micturition (secondary efficacy). Dose-response relationship was described by fitting a linear regression function tested for a non-zero slope with power of at least 80%. This made it reasonable to assume a sample size of at least 40 patients in each treatment arm.

Results

Of the 173 patients randomized, 43, 44, 47, and 39 individuals received placebo, or fesoterodine 4 mg, 8 mg, or 12 mg, respectively. 99 of these subjects had urodynamic confirmation of detrusor overactivity at baseline examination.

Multiple regression analysis showed statistically significant linear dose-response improvement from baseline and placebo in the primary efficacy variable of number of micturitions/24 hours (Table 1). ANCOVA for the number of urge urinary incontinence episodes per week shows that fesoterodine is significantly superior to placebo (p = 0.0396 for 4 mg, 0.0010 for 8 mg, and 0.0067 for 12 mg). The results are not influenced by the urodynamic status of patients. The change from baseline to end of treatment in the mean voided volume per micturition was 4.53mL in the placebo set, and 27.94mL, 58.69mL, and 92.34mL in the fesoterodine 4mg, 8mg, and 12mg groups, respectively. These secondary variables showed significant changes *versus* placebo as early as 2 weeks after randomization. Baseline urodynamic status did not influence the results.

Table 1. Analysis of covariance: Number of micturitions per 24 hours			
End of treatment	Fesoterodine 4 mg	Fesoterodine 8 mg	Fesoterodine 12 mg
Estimate for difference from placebo	– 0.996	– 1.815	– 1.784
Standard error for the difference	0.492	0.487	0.518
95% CI of the difference	– 1.97, – 0.02	– 2.78, – 0.85	– 2.81, – 0.76
P value (2-sided)	0.0446	0.0003	0.0007

Dry mouth, headache, and gastrointestinal symptoms were the more common adverse events. Ten of the patients (2, 1, 2, and 5 on placebo and fesoterodine 4 mg, 8 mg, and 12 mg, respectively) discontinued their medication due to adverse events. Dry mouth, the most common adverse event, was rated as mild to moderate in the majority of cases (Table 2). There were no clinically relevant changes in any of the measured vital signs.

Table 2. Occurrence and intensity of dry mouth *				
Treatment Group	Number of patients with dry mouth	Number of events		
		Mild	Moderate	Severe
Placebo (N = 43)	5	5	0	0
Fesoterodine 4 mg (N = 43)	16	10	6	0
Fesoterodine 8 mg (N = 47)	20	10	7	3
Fesoterodine 12 mg (N = 38)	14	9	3	2

* after randomization

Interpretation of results

Once-daily fesoterodine is efficacious in causing clinically relevant improvement in symptoms of OAB with a linear dose-response relationship irrespective of baseline urodynamic status.

Concluding message

- All 3 doses of fesoterodine led to significant and clinically relevant improvements from baseline in several parameters e.g., frequency, urge incontinence and voided volume per micturition.
- Improvements were seen as early as 2 weeks after randomization.
- Fesoterodine was generally well tolerated.

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