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A RANDOMIZED STUDY TO ASSESS THE ACTION OF FESOTERODINE ON URETHRAL FUNCTION IN WOMEN WITH STRESS URINARY INCONTINENCE USING URETHRAL PRESSURE REFLECTOMETRY

Hypothesis / aims of study

Pre-clinical studies in anesthetized dogs suggest that the active metabolite of fesoterodine (5-hydroxymethyl tolterodine which is also the active metabolite in man) increases maximum urethral pressure (MUP) (data on file).

Urethral Pressure Reflectometry (UPR) is a new technique for simultaneous measurements of pressure and cross-sectional area in the urethra. UPR provides a robust method for measuring the urethral opening and closing pressure and elastance (1-2). With this technique the pharmacological effect of norepinephrine reuptake inhibitors has been demonstrated in urethra and this effect has also been translated into improvements in SUI diary symptoms (3). In addition, UPR parameters have proven to be more sensitive and less variable than the conventional urethral pressure profile thereby requiring fewer subjects to evaluate a pharmacodynamic effect (3).

The aim of the study was to evaluate whether treatment with an antimuscarinic agent (fesoterodine) has an effect on urethral function in subjects with SUI using UPR. The primary outcome was the opening pressure and the secondary outcomes were the closing pressure and the urethral opening and closing elastance

Study design, materials and methods

The study was a Phase 2, randomized, double-blind, placebo-controlled, 3-period crossover study conducted in female subjects with urodynamically proven SUI.

The three treatments were: a) Fesoterodine 4 mg sustain release tablet, b) Fesoterodine 8 mg sustain release tablet and c) Placebo tablet. Each treatment period was of 7 days duration, with 7-10 days washout between treatment periods. An UPR measurement was performed before the first period and 4-8 hours after the last dose in each period.

Before the first period and during the last 3 days of each period the subject filled out a 3-day urinary diary.

The UPR examination was performed with the subject in the supine position with 150 ml saline in the bladder. Three successive measurements were made at each session and the mean of these triplicate measurements was used for analysis. The opening pressure, closing pressure, opening elastance, and closing elastance were obtained from the UPR examination.

A sample size of 18 subjects was needed to reach a power of 80% to detect a difference of 10 cmH_2O in the opening urethral pressure between active and placebo at a 2-sided significance level of 0.05 (assuming a within-subject SD of 9.9).

Participants were assigned randomization numbers sequentially as they were included in the study. According to a computer-generated randomization schedule the subjects received treatment regimens decided by their randomization number. Mirror replacement randomization numbers were used to replace withdrawn subjects.

An analysis of covariance (ANCOVA) model, with fixed effect terms for sequence, period and treatment, using baseline as a covariate, and subject within sequence as a random effect was used on the change from baseline in UPR endpoints, to test fesoterodine 4mg and 8mg vs placebo.

Results

A total of 22 women (age 34-64 years) were randomized and treated, 4 discontinued and one was excluded due to protocol violation. Thus 17 subjects were included in the per protocol analysis set (PPAS).

The results from the UPR examinations are shown in the table.

	Baseline Mean (SD)	Change from Baseline to Day 7 Adjusted Mean (SE)		
PPAS (n=17)	Pre-dose	Fesoterodine 4 mg	Fesoterodine 8 mg	Placebo
Opening pressure (cmH_2O)	50 (14.9)	-1.7 (1.3)	-0.6 (1.3)	-1.3 (1.3)
Closing pressure (cmH2O)	41 (14.4)	-2.5 (1.3)	-1.7 (1.3)	-1.8 (1.3)
Opening elastance (cmH2O/mm2)	1.9 (0.6)	-0.24 (0.13)	-0.07 (0.13)	-0.08 (0.13)
Closing elastance (cmH2O/mm2)	1.9 (0.6)	-0.26 (0.09)	-0.09 (0.09)	-0.07 (0.09)

No statistical significant difference between placebo and fesoterodine 4 mg or 8 mg

At baseline the mean number of stress urinary incontinence episodes per 24 hours was 1.4. The median reduction from baseline was 67% with fesoterodine 4 mg, 56% with fesoterodine 8 mg and 60 % with placebo. There was no meaningful difference between placebo and the active treatments.

The number of adverse events (AEs) reported following fesoterodine 4 mg (13) and placebo treatment (16) was similar while it was higher following fesoterodine 8 mg treatment (27). The majority of the AEs (82%) were mild in intensity, no treatment-related serious AEs were reported. Dry mouth was the most frequently reported AE. The incidence of dry mouth was more frequent following fesoterodine 8 mg (12 subjects) than fesoterodine 4 mg (3 subjects) or placebo (2 subjects).

Interpretation of results

Fesoterodine did not increase urethral pressure relative to placebo. The role of the muscarinic receptor in the control of urethral function in humans is unclear. The parameters measured by UPR showed no placebo effect while a large placebo effect was seen with the self reported stress urinary incontinence episodes.

The safety profile for fesoterodine was consistent with that observed in previous fesoterodine studies.

Concluding message

Fesoterodine does not have an effect on urethral function in patients with SUI. UPR offers an effective way of performing translation research for potential treatments in SUI.

References

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Was this study approved by an ethics committee?	**Yes**
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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**