114

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URETHRAL PRESSURE REFLECTOMETRY IS VALUABLE FOR EVALUATING PHARMACOLOGICAL THERAPIES FOR STRESS URINARY INCONTINENCE.

Hypothesis / aims of study

The efficacy of new pharmacological therapies should be established in the target organ in humans before the drug is introduced to the market. The target organ for stress urinary incontinence (SUI) is the urethra and a therapy for SUI should therefore demonstrate a clinical relevant influence on urethral closure function.

Urethral Pressure Reflectometry (UPR) is a new technique for simultaneous measurements of pressure and cross-sectional area in the urethra. Only a very thin and highly flexible plastic-bag is introduced into the urethra during the measurements. The cross-sectional area of the urethra is continually measured with sound waves while the pressure in the bag can be changed with a pump, thus the pressure needed to just open the closed urethra can be measured (opening pressure). In addition a stress-strain relationship for the urethra can be made from the simultaneous measurements of pressure and cross-sectional area. From the stress-strain relationship, biomechanical properties such as the elastance and the hysteresis of the urethra can be obtained. Thus UPR has the potential to demonstrate a pharmacological influence on urethral function. In addition, UPR parameters have proven to be more sensitive and less variable than the conventional urethral pressure profile (1) thereby requiring fewer subjects to evaluate a pharmacodynamic effect.

Esreboxetine is a highly selective norepinephrine reuptake inhibitor. 4 mg esreboxetine has a clinically significant effect on stress urinary incontinence (2). Esreboxetine is expected to increase the urethral pressure through the modulation of the central nervous system.

The aim of the study was to test if UPR could be used for developing and monitoring new pharmacological treatments for stress urinary incontinence in a phase one setting.

Study design, materials and methods

The study was a randomised double blinded placebo controlled cross-over study. The active treatment was 4 mg esreboxetine once daily oral dose. The treatment periods were 7-8 days separated by a wash-out period of 10 to 30 days. An UPR examination was performed before and 8 hours after the first dose and 8 hours after the last dose in each period.

Twelve continent healthy volunteers were screened and randomised, 6 (50%) subjects for each of the two treatment sequences 1) esreboxetine – placebo, 2) placebo – esreboxetine. Three subjects was excluded from the per protocol analysis as two were treated with prohibited concomitant medications (antibiotics for cystitis) and one was administered study medication in the incorrect order.

The UPR examination was made with the subject in the supine position with 150 ml saline in the bladder. The pressure in the plastic-bag was increased in steps of 5 cmH_2O until the plastic-bag was completely open. The pressure was then decreased in steps of 5 cmH_2O. Three successive measurements were made at each session. The opening pressure, closing pressure, opening elastance, closing elastance and the hysteresis were obtained from the UPR examination.

Prior to the study, data on the variability of UPR in continent women were limited, thus an interim analysis was performed after 12 women had completed the study. The data from the interim analysis showed that a power of over 80% would be obtained to detect a difference of 10 cmH_2O or more in the opening pressure between treatment means, at a 2-sided significance level of 0.05. Thus no increase to the sample size was required and recruitment was terminated after the interim analysis.

An analysis of covariance (ANCOVA) model, with terms for sequence, subject within sequence, period and treatment, using baseline as a covariate were used to analyse data for the per protocol analysis set.

Results

Out of the 12 subjects enrolled in the study, 9 were evaluable for the per protocol analysis set. The results of this analysis are shown in the table, the full analysis set reached the same conclusions as the per protocol analysis set.

	Post first dose		Post last dose	
	Placebo	Esreboxetine	Placebo	Esreboxetine
N	9	9	9	9
Opening pressure (cmH_2O)	89	113**	88	106*
Closing pressure (cmH_2O)	68	83 **	66	80*
Opening elastance (cmH_2O/mm^2)	2.4	2.1	2.3	2.3
Closing elstance (cmH_2O/mm^2)	2.3	2.6	2.2	2.4
Hysteresis (%)	21	23	22	22

The table shows the per protocol analysis. N=number of subjects.
All the results are the least squares means, adjusted for baseline. ** P < 0.01, *P<0.05

The maximal pressure increase in the opening pressure was seen after a single dose of esreboxetine (24 cmH_20 over placebo).

Forty-five adverse events occurred during the study (42 (93%) during esreboxetine, 3 (7%) during placebo). The majority of the adverse events were mild to moderate in severity with only one severe adverse event reported (whilst on placebo treatment). Hyperhidrosis and fatigue were the most frequently reported adverse events followed by dry mouth, dizziness, headache and nausea.

Interpretation of results

The opening and closing pressures increased significantly after both single and multiple doses of esreboxetine compared to placebo while the elastance and hysteresis were unchanged. The increased opening and closing pressures might explain the clinical effect of esreboxetine in SUI women (3). It is interesting to note that the maximum effect was seen after only one dose of esreboxetine. This observation raises the possibility that norepinephrine reuptake inhibitors may act both through a central pathway and also through a peripheral mechanism of action.

Concluding message

UPR seems to be valuable in developing and monitoring pharmacological therapies for SUI. Very few subjects are needed in a cross-over design study, when the opening pressure is used as endpoint, as the opening pressure has low variability. This study raises interesting questions about the primary site of action of norepinephrine reuptake inhibitors on urethral function and illustrates the importance of measuring the pharmacological effect directly in the target organ.

References

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What were the subjects in the study?	**HUMAN**
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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**