Measurement of Urethral Closure Function in Women With Stress Urinary Incontinence

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Purpose: We assessed the use of urethral pressure reflectometry in detecting pressure increases in the female urethra and compared the usefulness of urethral pressure reflectometry vs urethral pressure profilometry in a pharmacodynamic intervention study.

Materials and Methods: In this randomized, double-blind, placebo controlled, crossover study 17 women with stress urinary incontinence or mixed urinary incontinence received 4 mg esreboxetine or placebo for 7 to 9 days followed by a washout period before crossing over treatments. Urethral pressure reflectometry and urethral pressure profilometry were performed before and at the end of each treatment period.

Results: The urethral opening pressure measured with urethral pressure reflectometry increased significantly compared to placebo by 13.7 cm H2O (p < 0.0001) with an observed within subject standard deviation of 5.4. The increase in maximum urethral closure pressure was 8.4 cm H2O compared to placebo (p = 0.06) and for maximum urethral pressure the increase was 9.9 cm H2O (p = 0.04). However, the within subject SD for these parameters was higher at 11.4 and 12.2, respectively, implying lower power for these analyses. While receiving esreboxetine patients had significantly fewer incontinence episodes and reported a treatment benefit (global impression of change) compared to placebo.

Conclusions: The opening pressure measured with urethral pressure reflectometry was less variable compared to the parameters measured with urethral pressure profilometry (maximum urethral closure pressure and maximum urethral pressure). Consequently using urethral pressure reflectometry would result in a more efficient study design when investigating pharmacological effects on the urethra in future studies. We also found that esreboxetine was well tolerated, and had a positive and clinically relevant effect on urethral closure function and symptoms of stress urinary incontinence.

Key Words: urethra; urinary incontinence, stress; urodynamics

The European Medicines Agency Notes for Guidance (www.emea.europa.eu/pdfs/human/ewp/001801en.pdf) state that pharmacodynamic assessments should be performed early in the development of new pharmacotherapies for the treatment of SUI to demonstrate a relevant effect on urethral function. The parameter should be reproducible, thereby providing a reliable evaluation of a new compound in a small study. The European Medicines Agency recommends UPP and abdominal leak point pressure for the pharmacodynamic evaluation of drugs being developed for the treatment of SUI. However, these methodologies have low reproduc-

Abbreviations and Acronyms

AE = adverse event
CA = cross-sectional area
ICS = International Continence Society
IEF = weekly incontinence episode frequency
MUCP = maximum urethral closure pressure
MUP = maximum urethral pressure
PGIC = Patient Global Impression of Change
PPAS = per protocol analysis set
PVC = polyvinyl chloride
Qmax = maximum urine flow
RMSE = root mean square error
SUI = stress urinary incontinence
UPP = urethral pressure profilometry
UPR = urethral pressure reflectometry

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† Financial interest and/or other relationship with Pfizer.
urethra are not standardized and are neither sufficiently sensitive nor specific for routine use in the assessment of SUI.1

A novel method for the examination of the urethra is urethral pressure reflectometry, which measures urethral pressure and cross-sectional area simultaneously.2, 3 CA is measured by acoustic reflectometry. Using this technique a thin polyurethane bag is placed in the urethra during measurements. With this catheter-free technique the urethral pressure is measured while the urethra is almost completely closed. This offers a significant advantage compared to conventional techniques in which the urethra is dilated by a catheter during the measurement. UPR provides measures of the opening and closing pressure, opening and closing elastance, and hysteresis.3 4

Esreboxetine is a highly selective norepinephrine reuptake inhibitor. Following oral administration it is well absorbed, it crosses the blood-brain barrier and acts through the modulation of central nervous system norepinephrine nerve transmission. In healthy volunteers twice daily administration of 4 mg racemic reboxetine increased the maximum urethral closure pressure by 18% compared to placebo (Data on file, Pfizer, Inc). In this study we assessed the use of UPR in the detection of a pharmacologically induced pressure increase in the female urethra, and compared the usefulness of UPR and UPP in pharmacodynamic intervention studies.

MATERIALS AND METHODS

This was a randomized, double-blind, placebo controlled, crossover study. The subjects had a screening visit 1 to 2 weeks before period 1. At the first visit in period 1 subjects underwent baseline UPR and UPP assessments. Subjects then received 4 mg esreboxetine or placebo for 7 to 9 days followed by UPR and UPP assessments (period 1). After a washout period of 7 to 30 days the subjects received the other treatment, once again with UPR and UPP assessments before and after the treatment (period 2). In the last 3 days of each period the patients registered incontinence episodes in a daily diary. After each period the Patient Global Impression of Change was reported on a scale from 1 (very much improved) to 7 (very much worse) and the side effects were registered. Subjects had a safety followup assessment 7 to 9 days after completion of period 2.

Subjects

Inclusion criteria. The study included female outpatients 18 to 65 years old with symptoms of SUI presenting as pure SUI or stress predominant mixed urinary incontinence. At the screening visit urodynamic evidence of SUI was obtained.

Exclusion criteria. Patients were excluded from study if they had symptoms of SUI for less than 3 months, presence of nocturnal enuresis, neurological disease, urogenital prolapse grade 2 or greater, post-void residual urine greater than 50 ml, chronic local urogenital pathology, use of pharmacological agents or devices for urinary incontinence (excluding pads), or urinary tract infection. Patients with medical conditions or concomitant medication that contraindicated treatment with esreboxetine were also excluded from study.

Subjects were assigned to treatment sequences by a computer generated, pseudo random code. The sequences used were Sequence 1—4 mg esreboxetine succinate oral dose → matching placebo, Sequence 2—Placebo → esreboxetine succinate. A total of 22 women were screened and 3 did not meet the entry criteria while 1 withdrew consent. Thus, 18 females were randomized (table 1). One subject discontinued due to adverse events during the esreboxetine treatment, thus 17 subjects completed the study and were included in the PPAS.

Informed consent was obtained and the study was approved by the regional scientific ethical committee (KA-05077-GS). The study was disclosed on ClinicalTrials.gov (registration number NCT00141128).

Urethral Pressure Reflectometry Methodology

UPR has previously been described in detail.2–4 The methodology enables simultaneous measurement of pressure and CA along the entire length of the urethra. An empty, thin and distensible polyurethane bag was placed in the urethra. The plastic bag was connected to a pump and an acoustic device via a PVC tube. The polyurethane bag was inflated, thereby distending the urethra by pumping air into the bag at predetermined pressures. The CAs of the urethra were measured by acoustic reflectometry as modified by Klarskov et al.2 The minimal measurable CA was 0.4 mm2 and the maximum CA approximately 16 mm2. Pressure within the bag could be applied and measured from 0 to 200 cm H2O.

Patients were placed in a supine position and the bladder was emptied using a 10Ch catheter. After emptying the bladder 150 ml 9% NaCl at 37°C was instilled into the bladder. The polyurethane bag was placed in the urethra using a 5Ch baby feeding tube as a guide and the PVC tube was anchored to the meatus using Duoderm® plaster. To ensure the PVC bag was placed correctly it was inflated and deflated.

During the assessment the patients were resting and the pressure was increased in 5 cm H2O increments from 0 cm H2O until the polyurethane bag was fully inflated. Then the pressure was decreased in 5 cm H2O increments down to 0 cm H2O. At each of these steps the CA was measured for 3 seconds. The whole procedure was repeated 3 times with a 15-second pause between each series of measurements.

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics</th>
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<tbody>
<tr>
<td>Esreboxetine—Placebo</td>
</tr>
<tr>
<td>No. subjects</td>
</tr>
<tr>
<td>Mean age (range)</td>
</tr>
<tr>
<td>Mean kg wt (range)</td>
</tr>
<tr>
<td>Mean cm ht (range)</td>
</tr>
<tr>
<td>Mean yrs SUI (range)</td>
</tr>
</tbody>
</table>
opening pressure and the opening elastance were determined from the UPR measurements. Figure 1 shows and defines the parameters.

Urethral Pressure Profilometry

UPP was performed after the UPR measurements using the perfusion technique as described by Brown and Wickham, with Dantec Duet Multi-P equipment (Medtronic Functional Diagnostics, DK-2740, Skovlunde, Denmark). An 8Ch single lumen catheter with 2 side holes 5 cm from the tip was used for recording the urethral pressure in a lateral orientation. A withdrawal speed of 2 mm per second and a perfusion rate of 2 ml per minute were used. With this setting the maximum measurable rate of increase of pressure measured with blocked side holes was 61 cm H2O per second. Two successive profiles were obtained in the supine position with the patient relaxed. MUP and MUCP were determined from the UPP measurements taken.

Cystometry and Pressure Flow Study

Patients were assessed in a sitting position using a filling rate of 50 ml per minute. Two 5Ch water filled single lumen catheters were inserted for transurethral filling and pressure, respectively. An 8Ch catheter was inserted rectally. Coughing was performed for each 50 ml infused. If leakage was not demonstrated the cystometry was repeated with the patient in the standing position. The catheters were left in situ for pressure flow studies. Dantec Duet Multi-P equipment was used for measurements. A standard free-flow uroflowmetry (Urodyne® 1000) and residual urine measurement (Bladderscan® BVI 2500) were performed before each invasive urodynamic procedure.

End Points

The primary end point was opening pressure as measured by UPR after 7 days of treatment. The remaining parameters measured with UPR and UPP were secondary end points.

Statistics

Limited information is available on the variability of the primary end point, resting opening urethral pressure (assessed by UPR). The sample size estimation was consequently based on MUCP. MUCP had a within subject SD of 12.5 (RMSE) in a pilot study (Data on file, Pfizer, Inc) performed to evaluate the variability and reproducibility of MUCP in women with SUI. This variability was used for the power calculation.

Before the study a power calculation showed that 16 women were needed for the statistical test to have a power of 80% to detect a difference between treatment means, at a significance level of 0.05 (2-sided), with the assumption that MUCP would show an increase of 10 cm H2O following active treatment relative to placebo. However, this power calculation was miscalculated and the correct number should have been 27 women.

Analysis

To assess the effect of esreboxetine on urethral function the primary and secondary end points following the treatment were analyzed using an ANCOVA model, with terms for sequence, subject within sequence, period and treatment, and baseline measurement of the end point being analyzed. Proc GLM in SAS® was used to perform these analyses and, therefore, all of these terms were fitted as fixed effects. The comparison of interest was an oral dose of 4 mg esreboxetine vs placebo.

The analyses were performed on the PPAS. For the majority of the analyses the intent to treat and PPAS populations were the same, the rest differed only by 1 subject, hence only the PPAS results have been presented. Due to the exploratory nature of this study no adjustment of p value was made to account for inflation of the Type 1 error rate arising from testing multiple end points. All analyses were performed using SAS version 8.2 software.

Methods, definitions and units conform to the standards recommended by the ICS. However, the UPR measurements and parameters have not been included in the ICS standardization report.

Figure 1. UPR measurement from high pressure zone. Opening pressure (cm H2O) is defined as pressure where slope of flat part of curve intercepts with y-axis and is indicated by circle. Opening elastance (cm H2O/mm²) is slope of flat part of curve.
RESULTS

The observed treatment difference, within subject variability and standardized treatment difference for the opening pressure, MUCP and MUP are shown in table 2 together with the sample size calculation based on the variability observed in this study. The opening pressure has lower within subject variability than the MUCP and MUP (RMSE 5.4 compared to 11.4 and 12.2, respectively), resulting in smaller study design if this end point was used (7 compared to 23 and 26, respectively).

The changes after 7 days of treatment in UPR and UPP parameters and IEF are provided in table 3 with the PGIC scores. The opening pressure, opening elastance and the MUP were statistically significantly higher after the esreboxetine treatment compared to the placebo treatment. However, the increase in MUCP over placebo was not significant ($p /H11005 0.06$). The PGIC and IEF were significantly improved after the active treatment compared to placebo. For a minority of the end points there were significant sequence effects but no significant period effects. Further analysis of these end points for each sequence group separately has shown that the same conclusions were obtained for each sequence group except for MUCP. However, this seems to be due to the effect of 1 outlier. Figure 2 shows the individual subject profiles of the pre-dose and post-dose opening pressure, MUCP and MUP.

DISCUSSION

Variability of UPR and UPP

The variability observed for MUCP was slightly lower than the variability used in the original power calculation (RMSE 11.4 vs 12.5), but of a similar magnitude. However, for the primary end point of opening pressure as measured by UPR the observed within subject SD was considerably lower at 5.4 (RMSE). Based on the variability of MUCP found in the present study, sample size calculations show that 23 subjects would be required for a new study to have a power of 80% with an $\alpha$ of 0.05 to detect a difference of 10 cm H2O. In contrast, a study using opening pressure as the primary end point would require only 7 subjects to ensure the same power. This is probably due to the better reproducibility of the UPR technique, which has been documented previously. Thus, fewer subjects would need to be exposed to a new compound tested using the UPR technique, resulting in more efficient study designs compared to using MUCP and MUP as measured by UPP.

Urethral Pressure

Opening pressure was 13.7 cm H2O higher following esreboxetine treatment compared to placebo. For MUP and MUCP this increase compared to placebo

| Table 3. Efficacy results for the 17 women included in the PPAS |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo*</th>
<th>Esreboxetine*</th>
<th>Difference (95% CI)†</th>
<th>$p$ Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPR:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure (cm H2O)</td>
<td>45.2</td>
<td>58.8</td>
<td>13.7 (9.3, 18.0)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Opening elastance (cm H2O/mm²)</td>
<td>2.0</td>
<td>2.4</td>
<td>0.3 (0.1, 0.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCP (cm H2O)</td>
<td>48.6</td>
<td>57.0</td>
<td>8.4 (−0.4, 17.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>MUP (cm H2O)</td>
<td>64.5</td>
<td>74.4</td>
<td>9.9 (0.6, 19.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGIC (score)‡</td>
<td>3.5</td>
<td>2.4</td>
<td>−1.1 (−1.7, −0.5)</td>
<td>0.0009</td>
</tr>
<tr>
<td>IEF (No./wk)</td>
<td>14.2</td>
<td>5.9</td>
<td>−8.3 (−14.5, −2.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Values after the treatment period (least square mean from an ANCOVA appropriate for a 2×2 crossover study).
† Estimates based on comparison of least square means.
‡ The scale for PGIC went from 1 (very much improved) to 7 (very much worse) treated as a continous variable.
was 9.9 and 8.4 cm H2O, respectively. However, only MUP reached statistical significance. In an uncontrolled study the MUCP increased 6.5 cm H2O after 8 weeks of treatment with 80 mg duloxetine daily.8

**Urethral Elastance**

The elastance (dP/dV) is the inverse of compliance and is defined as the resistance of an object to deformation by an external force. It determines how much the urethra will open in response to a bladder pressure greater than the urethral pressure.3 Elastance is significantly decreased in women with SUI compared to continent women.9 The opening elastance increased significantly during the esreboxetine treatment compared to placebo, and may contribute to improved urethral closure function and subsequent improvement in the symptoms of SUI. In men an α-adrenoceptor antagonist (tamsulosin) has shown significantly decreased elastance at the bladder neck without any change in opening pressure.10

**Efficacy**

Patients had 58% less incontinence episodes during the active treatment compared to the placebo period. Esreboxetine demonstrated a similar treatment benefit in an 8-week study.11 In placebo controlled randomized studies patients on duloxetine experienced approximately 25% to 40% less incontinence episodes compared to those on placebo.12–15 However, the efficacy of esreboxetine and duloxetine cannot be compared on the basis of these data because of significant differences in the designs, the treatment periods and the number of subjects included in the studies. The patients also had a significant improvement in the PGIC score in the active period compared to the placebo period.

**Safety**

The frequency of adverse events seen in this study is commensurate with the mechanism of action of esreboxetine. In the short treatment period esreboxetine was considered to be safe as all the adverse events were mild. The Qmax decreased and the post-void residual urine increased during active treatment. However, the changes were not clinically significant.
CONCLUSIONS
The opening pressure measured with UPR was less variable compared to the parameters measured with UPP (MUCP and MUP). Thus, using UPR would result in a more efficient study design when investigating pharmacological effects on the urethra in future studies. The study also showed that esreboxetine is well tolerated and has a positive effect on urethral closure function as well as on the symptoms of SUI.

REFERENCES

EDITORIAL COMMENT
This is the fifth report in an ongoing project from this group investigating urethral pressure reflectometry as a means of measuring urethral function in the female. Their cumulative work (all referenced in this article) has shown that at this center UPR is a viable, easily performed assessment of female urethral function which not only provides better discrimination between healthy women and those with stress incontinence than conventional urethral pressure profiles, but also provides parameters that have a sound, physiological basis, and are more reproducible and more sensitive to change than UPPs.

In 2002 the ICS reported that the clinical usefulness of urethral pressure measurements was unclear, and that “There is no doubt that the urethral pressure is of significant importance for the continence mechanism.” UPR is an exciting, important development that may provide the optimal way to characterize urethral closure in terms of pressure.

Gordon Hosker
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Saint Mary’s Hospital
Manchester, United Kingdom

REFERENCE