THE EFFECTS OF α1A ADRENOCEPTOR INHIBITORS ON THE URETHRAL PERFUSION PRESSURE OF FEMALE RATS

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ABSTRACT

Objectives: This study was performed to assess the effects of α1A adrenoceptor antagonists on urethral perfusion pressure (UPP) and their therapeutic potential for female bladder outlet obstruction (BOO).

Methods: A cannula was inserted into the femoral arteries of female rats to administer tamsulosin (treatment I), doxazosin (treatment II) or phentolamin (treatment III) and to monitor systemic blood pressure. Tamsulosin was also administered to male rats (group IV). UPP and vesical pressures (Pves) were monitored using a triple-lumen catheter.

Results: After administration of tamsulosin to group I, frequency decreased significantly, and the duration of minimal urethral relaxation with high-frequency oscillations (Dhfo) was significantly prolonged. With the exception of mean arterial blood pressure (MAP), none of the parameters of group I differed significantly from those of group II and group III. The change to MAP after tamsulosin administration was significantly lower than after doxazosin or phentolamin administration. With the exception of maximal Pves, which was significantly higher in males (group IV) than in females of group I, UPP and Pves curves of male rats were similar to those of females before administration of tamsulosin. The prolonged frequency and Dhfo in group IV after administration of tamsulosin to males was significantly different from that of females.

Conclusions: The α1A adrenergic receptor may be a functional subtype in the female rat urethra. α1A adrenoceptor antagonists prolonged Dhfo and decreased the frequency of involuntary bladder contraction. It is possible that administration of α1A adrenoceptor antagonists would not only improve obstructive symptoms, but also ameliorate irritative symptoms by prolonging Dhfo and the frequency of involuntary bladder contractions. (Continence 1: 42-48, 2005)

Key Words: α1A adrenoceptor antagonist, Urethral perfusion pressure, Tamsulosin

Alpha-adrenergic antagonists have been used for treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Proximal urethral tone in the human is maintained largely by activation of postsynaptic α-adrenoceptors.1,2 Therefore, α-adrenergic antagonists decrease proximal urethral tone and improve LUTS. However, they may have adverse cardiovascular effects such as orthostatic hypotension.3 Two subtypes of the α-adrenoceptor (α1 and α2) have been described, and molecular cloning studies have identified three subtypes of the α1-adrenoceptor. It has been reported that mRNA that encodes the α1A adrenoceptor is predominant in the human prostate. Tamsulosin is an α1 antagonist and is administered once daily. It exhibits a higher degree of selectivity for the α1A receptor than the α1B adrenoceptor, but does distinguish between the α1A and α1D adrenoceptors.4-6 This feature is unique to tamsulosin.

The causes of female voiding dysfunction, including urinary retention, are various. In some cases without bladder outlet obstruction, large volumes of postvoiding residual urine are present. The main cause of female urinary retention is detrusor underactivity rather than outlet obstruction. Although the exact incidence of detrusor underactivity has not been measured, it is estimated to be responsible for 2.7–8% of female lower urinary tract symp-
Kumar and coworkers reported that 50% of female LUTS patients displayed an improvement of their symptoms after administration of α-adrenergic antagonist. Functional bladder neck obstruction in women remains a poorly understood and improperly diagnosed clinical entity. These are usually not diagnosed as such and are treated as cases of urethral syndrome, lazy bladder, or non-neurogenic bladder. During the past few years, definitive diagnosis of functional bladder neck obstruction has been accomplished using detailed synchronous pressure flow, electromyography and video urodynamics. The efficacy of α-adrenergic antagonists in such female patients has not been established. Several studies have demonstrated that the female bladder neck is contracted by α-adrenoceptor stimulation. These results suggest that α1A adrenoceptor antagonists may represent an effective treatment for functional bladder outlet obstruction (BOO) in females, but detailed in vivo studies are lacking. This study was performed to identify the effects of an α1A adrenoceptor antagonist on urethral perfusion pressure (UPP) and to assess its therapeutic potential for female BOO.

MATERIALS AND METHODS

Preparation of animals
Thirty mature Sprague-Dawley female white rats weighing 200–250 g were randomized into three groups of 10, each of which was treated with tamsulosin (group I), doxazosin (group II) or phentolamin (group III). Tamsulosin was also administered to 10 male rats (group IV). Polyethylene catheters (Clay-Adams PE-10) for infusion of drugs and monitoring of systemic blood pressure were inserted into the femoral arteries and advanced to the bifurcation of the aortas. This was performed under general anesthesia by intraperitoneal administration of 20% (w/v) urethane. Tracheotomy was performed to facilitate respiration.

Monitoring of UPP and intravesical pressure
Animal models were prepared using a modification of the method of Jung et al. After exposure of the bladder and proximal urethra via a midline abdominal incision, urethral perfusion pressure was monitored using a custom-designed triple-lumen catheter, which consisted of an outer catheter (a no. 8 French cut-down tube) containing two polyethylene catheters of different sizes (Clay-Adams PE-160 and PE-50) connected to a pipette tip (Figure 1). This was introduced transvesically through an incision in the bladder dome, and the pipette tip was placed securely in the bladder neck. The outer lumen was connected to a polygraph (Grass polygraph Model 7E, Quincy, MA, USA) to monitor intravesical pressure. The middle lumen (PE-160) was connected to a Harvard infusion pump for continuous saline infusion. The inner lumen (PE-50) was connected to the polygraph through a pressure transducer and used to monitor urethral pressure. After a 30-minute postsurgical stabilization period, the bladder was filled with 0.7–1.0 mL of normal saline via the outer lumen of the catheter, and isovolumetric pressure was recorded throughout the experiment. The urethra was continuously infused with warm saline (37°C, 0.075 mL/min) in an antegrade manner using a Harvard infusion pump. The infused saline was allowed to drain freely through the urethral meatus. Thus, isovolumetric bladder pressure and UPP were recorded independently and simultaneously. Changes of intravesical pressure and urethral perfusion pressure were monitored after administration of each experimental drug.

Statistical analysis
All data are reported as means±standard deviations. Means were compared by paired t test or one-way ANOVA. A probability of P<0.05 was deemed to be significant.

RESULTS

Intravesical pressure and UPP before drug administration
Before drug administration, urinary bladders exhibited periodic contractions with a pressure intensity of 54.4±12.2 cm H2O and a frequency of 0.44±0.23 min⁻¹. UPP varied according to vesical contractions. Baseline UPP was 28.4±4.0 cm H2O. UPP decreased to 8.2±3.2 cm H2O before intravesical contractions and oscillated periodically.
Changes in female rats after administration of tamsulosin

The minimal concentration of tamsulosin required to evoke maximal changes in UPP in Group I was $10^{-7}$ M. After administration of 0.1 mL $10^{-7}$ M tamsulosin, baseline UPP before urethral relaxation (UPPbasal) was decreased by $1.3 \pm 1.0$ cm H$_2$O, but this change was not statistically significant (Figure 3, Table 1, $P > 0.05$). The frequency of bladder contraction was decreased significantly from $0.44 \pm 0.23$ to $0.32 \pm 0.18$ min$^{-1}$ ($P < 0.01$), and the duration of urethral relaxation with high-frequency oscillations (Dhfo) was prolonged significantly from $33 \pm 6$ to $44 \pm 8$ s by tamsulosin injection ($P < 0.01$). UPP during urethral relaxation (UPPmin) was not decreased ($P > 0.05$). Changes of mean arterial pressure (MAP) were not significantly different in pre- and post-tamsulosin administration ($P > 0.05$).

Changes after administration of doxazosin and phentolamin

Minimal drug concentrations (in 0.1 mL injection volumes) required for induction of maximal changes of UPP were $0.5 \pm 10^{-6}$ M for doxazosin (Group II) and $10^{-5}$ M for phentolamin (Group III). Changes in intravesical pressure and UPP after administration of these drugs were similar to those after administration of tamsulosin. UPPbasal and UPPmin were not significantly changed. The frequency of bladder contraction was significantly decreased and Dhfo was significantly prolonged in both groups. The changes after doxazosin or phentolamin administration were not significantly
Table 1. Changes of parameters before and after tamsulosin administration in female rat. Frequency was significantly decreased and duration of high frequency oscillation was prolonged after tamsulosin administration.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Differences</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (/min)</td>
<td>0.44±0.23</td>
<td>0.32±0.18</td>
<td>-29.5%</td>
<td>P&lt;0.01*</td>
</tr>
<tr>
<td>UPPbasal (cmH₂O)</td>
<td>28.4±4.0</td>
<td>27.1±4.7</td>
<td>-4.5%</td>
<td>NS</td>
</tr>
<tr>
<td>UPPmin (cmH₂O)</td>
<td>8.2±3.2</td>
<td>8.0±2.5</td>
<td>-2.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Dhfo (sec.)</td>
<td>33±6</td>
<td>44±8</td>
<td>-34%</td>
<td>P&lt;0.01*</td>
</tr>
<tr>
<td>Pvesdif (cmH₂O)</td>
<td>54.4±12.2</td>
<td>51.9±13.5</td>
<td>-5.8%</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>97.8±7.5</td>
<td>95.6±8.5</td>
<td>-2.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

UPPbasal, baseline urethral perfusion pressure during contraction; UPPmin, minimal urethral perfusion pressure during relaxation; Dhfo, duration of high frequency oscillation; Pvesdif, vesical pressure change between peak and baseline pressure; MAP, mean arterial pressure; *, statistically significant; NS, not significant.

Table 2. Changes of parameters before and after various α-adrenoceptor antagonist in female rats. There were no significant differences inter-groups except mean arterial pressure change.

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin (group I)</th>
<th>Doxazosin (group II)</th>
<th>Phentolamin (group III)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFrequency (/min)</td>
<td>-0.12±0.03</td>
<td>-0.10±0.05</td>
<td>-0.14±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>ΔUPPdif (cmH₂O)</td>
<td>-1.1±0.3</td>
<td>-1.3±0.5</td>
<td>-1.3±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>ΔDhfo (sec.)</td>
<td>11±6</td>
<td>12±5</td>
<td>11±6</td>
<td>NS</td>
</tr>
<tr>
<td>ΔPvesdif (cmH₂O)</td>
<td>2.5±0.5</td>
<td>3.9±1.1</td>
<td>2.9±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>ΔMAP (mmHg)</td>
<td>-1.5±0.4</td>
<td>-9.6±3.9</td>
<td>-13.5±4.9</td>
<td>P&lt;0.05*</td>
</tr>
</tbody>
</table>

ΔFrequency, frequency change before vs. after medication; ΔUPPdif, change of amplitudes of urethral perfusion pressure after medication; ΔDhfo, change of duration of high frequency oscillation after medication; ΔPvesdif, change of amplitudes of vesical pressure after medication; ΔMAP, change of mean arterial pressure after medication; NS, not significant; *, statistically significant.

Figure 4. Effect of tamsulosin on bladder and urethral pressure in a male rat. Urethral perfusion pressure and vesical pressure changes were similar to that of female rats with the exception that maximal vesical pressure was significantly higher in males. After tamsulosin treatment, frequency was significantly decreased, and duration of bladder contraction and urethral relaxation with high-frequency oscillations were significantly prolonged.

Changes in male rats after administration of tamsulosin
Baseline UPP and intravesical pressure curves of male rats (group IV) were similar to those of female rats (Figure 4). However, maximal Pves, UPPbasal, and UPPmin (80±6.7, 32.3±5.3 and
frequency oscillation after tamsulosin; amplitudes of vesical pressure after tamsulosin; 46
Sympathetic outflow from the rostral lumbar detrusor wall layer as well as in the pelvic plexus. Ionic neurons in humans are located in the bladder body and contraction of the bladder outlet and urethra, which results in the storage of urine in the bladder.12

The external urethral sphincter (EUS) motor neurons are located along the lateral border of the ventral horn. The bladder-to-EUS guarding reflex that triggers sphincter contractions during bladder filling could, in turn, activate sphincter muscle afferents that initiate inhibition of the parasympathetic excitatory pathway to the bladder. Thus, a bladder-to-sphincter-to-bladder reflex pathway could, in theory, contribute to suppression of bladder activity during urine storage.13

Alpha-adrenoceptor antagonists relax the bladder outlet and improve urinary flow in BPH patients by reducing prostatic smooth muscle tone through the blockade of sympathetic adrenergic receptors. However, the effect of α-adrenoceptor antagonists on patients with LUTS and females with bladder outlet obstruction is not well established. Since Gallagher et al14 described lower urinary tract symptoms including frequency, urgency, and suprapubic discomfort in women, this female urethral syndrome has been only vaguely defined, resulting in much controversy. However, female urethral syndrome still draws the attention of many clinicians because there are a significant number of patients that report with this problem. Because no definition of this syndrome exists and a clear mechanism has not yet been elucidated, there is a lack of objective data and no agreement on treatment. Currently, patients are treated according to the individual doctor's personal experience.15,16 There are multiple causes of female bladder outlet obstruction. These include dysfunctional voiding syndrome, external sphincter spasticity, and detrusor sphincter dyssynergia. Dysfunctional voiding syndrome of detrusor sphincter dyssynergia in the absence of a neurological lesion is known as Hinman's syndrome. The hallmark of the syndrome is voiding difficulty due to psychogenic causes, and Hinman and Baumman hypothesized that the etiology was dyssynergic external urinary sphincter activity. External sphincter spasticity may be caused by vaginitis, urethritis, perirectal gland abscess, and any other condition that causes inflammation around the external sphincter. Patients may develop acute urinary retention or recurrent cystitis.17 Detrusor sphincter dyssynergia exists in patients who have an abnormality in pathways between the spinal cord and the brain stem pontine micturition center, such as spinal cord injury, multiple sclerosis, and various forms of transverse myelitis.

In female patients, LUTS may cause obstructive and irritative symptoms. A variety of treatments

Table 3. Changes of parameters before and after tamsulosin treatment in female and male rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Female</th>
<th>Male</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (1/min)</td>
<td>-0.12±0.03</td>
<td>-0.18±0.07</td>
<td>P&lt;0.05*</td>
</tr>
<tr>
<td>ΔUPPdif (cmH2O)</td>
<td>-1.1±0.3</td>
<td>-1.0±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>ΔDhfo (sec.)</td>
<td>11±6</td>
<td>16±4</td>
<td>P&lt;0.01**</td>
</tr>
<tr>
<td>ΔPvesif (cmH2O)</td>
<td>2.5±0.5</td>
<td>3.1±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>-1.5±0.4</td>
<td>-1.0±0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

ΔFrequency, frequency change before and after tamsulosin; ΔUPPdif, change of amplitudes of urethral perfusion pressure after tamsulosin; ΔDhfo, change of duration of high frequency oscillation after tamsulosin; ΔPvesif, change of amplitudes of vesical pressure after tamsulosin; MAP, change of mean arterial pressure after tamsulosin; NS, not significant; *, statistically significant.

13.7±6.2 cm H2O, respectively) were significantly higher than that of group I (P<0.05). The frequency (0.67±0.31 min⁻¹) was also significantly higher than that of group I (P<0.05). Frequency and Dhfo were significantly prolonged by administration of tamsulosin to group IV, and these changes were more significant than those in group I (Table 3). MAP was 100.8±6.5 mm Hg and was not changed after tamsulosin administration.

DISCUSSION

The micturition process can be visualized as a complex of neural circuits in the brain and spinal cord, which coordinate the activity of smooth muscle in the bladder and urethra. These circuits act as on/off switches that alternate the state of the lower urinary tract between one of storage and one of elimination.11

Parasympathetic preganglionic neurons (PGN) innervating the lower urinary tract are located in the lateral part of the sacral intermediate gray matter in a region termed the sacral parasympathetic nucleus (SPN). Parasympathetic PGN send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter acetylcholine. Parasympathetic postganglionic neurons in humans are located in the detrusor wall layer as well as in the pelvic plexus.

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and urethra. Activation of sympathetic nerves induces relaxation of the bladder outlet and urethra, which results in the storage of urine in the bladder.12

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traction was also decreased by study, the frequency of involuntary bladder con-
tractions. It is possible that an α-adrenoceptor antagonist would not only improve obstructive symptoms, but also ameliorate bladder irritative symptoms by prolonging the duration of high-frequency oscillations and the frequency of involuntary bladder contractions.

CONCLUSIONS

The q₁A adrenoceptor may be the functional subtype in the female rat urethra. q₁A adrenoceptor antagonists prolonged the duration of high-frequency oscillations and decreased the frequency of involuntary bladder contractions. It is possible that an α₁A adrenoceptor antagonist would not only improve obstructive symptoms, but also ameliorate bladder irritative symptoms by prolonging the duration of high-frequency oscillations and the frequency of involuntary bladder contractions.

REFERENCES