EFFECTS OF A NEW PHOSPHODIESTERASE 5 INHIBITOR, MIRODENAFIL, ON THE FEMALE RAT BLADDER IN A PARTIAL BLADDER OUTLET OBSTRUCTION MODEL: PHYSIOLOGICAL AND IMMUNOHISTOCHEMICAL ASPECTS

Hypothesis / aims of study
We investigated the effects of mirodenafil, new phosphodiesterase-5 inhibitor developed in Korea, on the female rat bladder in a partial bladder outlet obstruction (BOO) model through cystometry and immunohistochemistry.

Study design, materials and methods
Thirty six female Sprague-Dawley rats (body weight, 200-300 g) were divided into 4 groups; the control group (sham-operation), BOO-no medication group (BOO for 2 weeks), BOO-1mg/kg group (mirodenafil medication at 1mg/kg after BOO), BOO-4mg/kg group (mirodenafil medication at 4 mg/kg after BOO). To obtain a partial obstruction of the urethra, we modified the method of Mattiason and Uvelius. The rats of BOO-1mg/kg and BOO-4mg/kg groups were orally fed with mirodenafil once daily for 2 weeks. Two weeks later, the rats of each group underwent cystometry under urethane anesthesia. A PE-50 catheter was inserted into the bladder through the bladder dome and connected to a pressure transducer and a syringe pump for infusing saline using a three-way stopcock. After cystometry, the bladder was excised to perform immunohistochemical staining for connexin 43 and Rho-kinase.

Results
The 3 BOO groups induced a significant increase in bladder weight compared to the control group. Baseline pressure, threshold pressure and maximum voiding pressure were not different between the 4 groups. Voiding intervals were significantly reduced in the 3 BOO groups compared to the control group (p<0.05). The interval was prolonged in the 2 mirodenafil medication groups compared to BOO-no medication group (p<0.05) (Table). On immunohistochemical examination, connexin 43 was localized in the submucosal area. Staining intensity increased in the 3 BOO groups compared with the control group, but decreased in the 2 mirodenafil medication group compared to the BOO-no medication group. The results of Rho-kinase staining were similar to those of connexin 43 staining.

Interpretation of results
Mirodenafil can increase the voiding intervals of female rats in a partial BOO model. It also decreases the expression of connexin 43 and Rho-kinase. The decrease of bladder overactivity by mirodenafil may correlate intracellular communication through connexin 43 and PDE-5 inhibitor-induced cGMP might decrease bladder overactivity through Rho/Rho-kinase mechanism.

Concluding message
Mirodenafil could be a possible option for the treatment of overactive bladder.

Table. Cystometric parameters in each group

<table>
<thead>
<tr>
<th>Group</th>
<th>BPr (cmH2O)</th>
<th>ThPr (cmH2O)</th>
<th>ThPr-BPr (cmH2O)</th>
<th>MVP (cmH2O)</th>
<th>Contraction interval (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=8)</td>
<td>5.2±4.5</td>
<td>9.6±6.7</td>
<td>4.4±2.7</td>
<td>33.3±5.7</td>
<td>421.6±88.0</td>
</tr>
<tr>
<td>BOO-no mx (n=9)</td>
<td>4.3±4.4</td>
<td>8.0±6.1</td>
<td>3.7±2.0</td>
<td>31.4±8.9</td>
<td>92.4±37.6</td>
</tr>
<tr>
<td>BOO-1mg/kg (n=9)</td>
<td>3.8±5.2</td>
<td>8.1±5.6</td>
<td>4.3±1.9</td>
<td>42.7±18.1</td>
<td>151.2±69.7</td>
</tr>
<tr>
<td>BOO-4mg/kg (n=8)</td>
<td>5.3±4.8</td>
<td>10.0±4.9</td>
<td>4.7±1.2</td>
<td>43.9±24.5</td>
<td>228.4±55.1</td>
</tr>
</tbody>
</table>

BPr: baseline pressure, ThPr: threshold pressure, MVP: maximum voiding pressure
*p<0.05 (vs control), +p<0.05 (vs BOO no medication).

Specify source of funding or grant
Eulji University research grant, 2009

Is this a clinical trial?
No

What were the subjects in the study?
ANIMAL

Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?
Yes

Name of ethics committee
This study was approved by Institutional Animal Care and Use Committee of Clinical Research Institute, Seoul National University Hospital. (No. 07-0205)