New Treatment Modalities for Benign Prostatic Hyperplasia

Seung-June Oh, MD
Department of Urology,
Seoul National University Hospital
Options for Treating BPH

- Pharmacotherapy
  - α blocker
  - Agents for BPH + OAB
  - Phytotherapy

- Intraprostatic injection:
  - Anhydrous ethanol
  - Botulinum toxin
  - Others

- Less invasive Tx
  - Thermotherapy
  - Laser
  - Others

- Invasive Tx
  - TUR-P
  - Open prostatectomy
  - Others
Human Adrenoceptors (ARs)

- **Types**
  - \( \alpha_1 \): 1A, 1B, 1D
  - \( \alpha_2 \): 2A, 2B, 2C
  - \( \beta \): 1, 2, 3

- **\( \alpha_1 A \)-AR**
  - Predominant in human prostatic stroma
  - Dynamic component of obstruction and related voiding symptoms

- **\( \alpha_1 D \)-AR**
  - Predominantly expressed in the bladder
  - Regulating detrusor contractility and bladder function in storage phase
  - Partly contributes to the OAB 2° to BPO
  - Exact mechanism: unknown
Pharmacotherapy: $\alpha$ blocker

- Nonsubtype selective $\alpha_1$-AR blocker
  - Terazosin
  - Doxazosin
  - Alfuzosin

- Subtype selective $\alpha_1$-AR blocker
  - Tamsulosin $\alpha_1A/1D$-AR blocker ($\alpha_1A>1D$)
  - Naptopidil: $\alpha_1A/1D$-AR blocker ($\alpha_1A<1D$)
  - Silodosin: $\alpha_1A$-AR blocker
  - Others
Naftopidil

- Newly synthesized α blocker (KT 611)
- Phenyl piperazine derivative
- 50-75 mg p.o. qd
- In the Japanese market since 1999
- Commercial name
  - Flivas Tablet 25, 50mg (Flivas Tablet 25, 50mg)
  - Avishot Tablet 25, 50mg (Avishot Tablet 25, 50mg)
Naftopidil: *in vitro* study (1)

- Mesenteric and carotid arteries (dog); thoracic aortae (rabbit, guinea pig and rat)

- Mechanism of action: $\alpha_1$-AR antagonist

Muramatsu I at al. Jpn J Pharmacol. 1991
Using cloned human $\alpha_1$-adrenoceptor subtypes

Selective for the $\alpha_1\text{D}$-AR with approximately 3- and 17-fold higher affinity than for the $\alpha_A$- and $\alpha_1\text{B}$-AR subtypes, respectively.

Takei R et al. Jpn J Pharmacol. 1999
Naftopidil: *in vivo* study

- i.v. administration of naftopidil, tamsulosin and prazosin in an anesthetized dog model
- Antagonist potency against Phe-mediated increases in prostatic pressure and mean BP
- Selectivity index: naftopidil (3.7), tamsulosin (1.2), prazosin (0.6)

Takei R et al. Jpn J Pharmacol 1999
Naftopidil appears to have been effective in the short-term treatment of BPH.

Naftopidil: Clinical study (2)

Predominant efficacy on storage symptoms as well as voiding symptoms associated with BPH.

Effective for nocturia in patients with BPH regardless of the existence of nocturnal polyuria.

Naftopidil and tamsulosin provided similar efficacy in the treatment of LUTS with BPH. However, naftopidil was better than tamsulosin for nocturia.

Nishino Y et al. BJU Int. 2006
**Efficacy on BPH Storage Symptoms**

- **Predominant** α1D-AR in the human bladder  

- **Increase in** α1D-AR expression in obstructed and hypertrophied rat bladder  

- **Nonselective** α1-AR antagonist is effective for storage symptoms  

- **Naftopidil inhibits micturition reflex by acting on** α1D or α1A-AR in the LS spinal cord  
  (Sugaya K et al. Neurosci Lett 2002)
Silodosin (KMD-3213)

- Urief® capsule mg, mg (Kissei 薬 会 )
- 4mg po bid
-  (2006. 1.)
Silodosin: Effect on the NE-induced Rabbit Prostate Contraction

Tatemichi S et al. α1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213) [Yakugaku Zasshi. 2006]
Silodosin: Receptor Subtype Selectivity

- Mouse-derived α1 AR- cell (3 human AR expressed)
- higher selectivity for the α1A-AR subtype than tamsulosin, naftopidil or prazosin

Table 1. Affinity and Selectivity for Human α1-AR Subtype of Silodosin and Other α1-AR Antagonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>α1A-AR (nmol/l)</th>
<th>α1B-AR (nmol/l)</th>
<th>α1D-AR (nmol/l)</th>
<th>α1-AR subtype selectivity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>α1A/α1B ratio</th>
<th>α1D/α1B ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silodosin</td>
<td>0.039±0.006</td>
<td>6.5±0.6</td>
<td>2.2±0.1</td>
<td>162</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>Tamsulosin hydrochloride</td>
<td>0.012±0.002</td>
<td>0.12±0.00</td>
<td>0.030±0.005</td>
<td>9.55</td>
<td>3.80</td>
<td></td>
</tr>
<tr>
<td>Naftopidil</td>
<td>23±7</td>
<td>7.8±0.0</td>
<td>4.4±0.4</td>
<td>0.372</td>
<td>1.78</td>
<td></td>
</tr>
<tr>
<td>Prazosin hydrochloride</td>
<td>0.12±0.01</td>
<td>0.028±0.002</td>
<td>0.078±0.007</td>
<td>0.204</td>
<td>0.316</td>
<td></td>
</tr>
<tr>
<td>WB4101 hydrochloride</td>
<td>0.17±0.01</td>
<td>1.1±0.1</td>
<td>0.22±0.04</td>
<td>6.03</td>
<td>5.01</td>
<td></td>
</tr>
<tr>
<td>BMY7378 dihydrochloride</td>
<td>75±21</td>
<td>28±7</td>
<td>0.43±0.06</td>
<td>0.389</td>
<td>64.6</td>
<td></td>
</tr>
</tbody>
</table>

The Ki value in the Table presents the mean ± standard error of 3 experiments. <sup>a</sup> The subtype selectivity (α1A/α1B and α1D/α1B ratios) was calculated from the ratio after converting the concentration, specifically, using 10<sup>M</sup> [M=pKi (α1A or α1D) − pKi (α1B)].

Tatemichi S et al. α1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213)] Yakugaku Zasshi. 2006
Silodosin: Tissue selectivity

- Mouse-derived α1 AR- cell (3 human AR expressed)
- Selectivity for lower urinary tract was higher for silodosin than for the other α1-AR antagonists

<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>Selectivity for the lower urinary tracta)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silodosin</td>
<td></td>
<td>282</td>
</tr>
<tr>
<td>Tamsulosin hydrochloride</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Naftopidil</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Prazosin hydrochloride</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

a) The selectivity for the lower urinary tract means the ratio after converting the concentration, specifically, using 10^θ (M= pA2 or pKb (prostate, urethra or trigone of bladder)− pA2 (spleen or aorta)).

Tatemichi S et al. α1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213)] Yakugaku Zasshi. 2006
Silodosin: Phase II dose-finding study

- **Study design**
  - Placebo-controlled, double-bind, parallel group comparative study

- **Subject**
  - BPH patients with LUTS

- **Dosage and Administration**
  - 4 mg/day (n=86), 8 mg/day (91) or placebo (89)
  - Twice a day dosing (morning and evening)

- **Treatment period**
  - 4 weeks
Silodosin: IPSS total score & QoL score at end-point

### Change from baseline in IPSS total score

- **Placebo**: 
  - Baseline: -7
  - Change: 0

- **4mg/day**: 
  - Baseline: -6
  - Change: -1.2
  - *p* = 0.0126

- **8mg/day**: 
  - Baseline: -5
  - Change: -1.4
  - *p* = 0.0000

### Change from baseline in QoL score

- **Placebo**: 
  - Baseline: 0
  - Change: 0

- **4mg/day**: 
  - Baseline: -0.2
  - Change: -0.6
  - *p* = 0.0451

- **8mg/day**: 
  - Baseline: -0.4
  - Change: -1.4
  - *p* = 0.0009

*Note: Baseline scores are as follows: Placebo = -7, 4mg/day = -6, 8mg/day = -5.*
Changes in Qmax up to 52 weeks (Silodosin Extended)

Mean Changes in Qmax

Only patients who continuously entered the long term study (KMD-203) with the blind maintained.
Urapidil

- α1A-AR selective
- Prospective placebo-controlled multicentric double-blind trial
- 214 BPH patients: 4 groups (placebo, 15 mg/d, 60 mg/d, 90 mg/d)
- Day and night urinary frequency, Qmax improved significantly (p < 0.05)
- More patients in 90 mg/d group (7/55) and 60 mg/d group (4/51) had side effects

Kawabe K et al. Urol Int. 1993
α1 Antagonists Still in the Bench

- WB 4101 hydrochloride
- BMY 7378 dihydrochloride
- RS-17053
- Niguldipine
Advantages (in general):
Botulinum Toxin (BTX) Injection

- Systemic pharmacologic effects are rare.
- Permanent destruction of tissue does not occur.
- Graded degrees of relaxation may be achieved by varying the dose injected.
- Most adverse effects are transient.
- Patient acceptance is high.
1877
1832
First TP injection for prostatitis

TP & TR puncture for prostatic abscess

1910
1936
1970
1988
Evidence of extra prostatic leakage with TP injection

Human TP injection for BPH with Pepsin Pregl's solution

1966
TP injection revisited using absolute ethanol for prostatic indication

Landmark study published using TP injection for BPH

1998
Passive deflection needle for TU injection

2003
2000
TP Botox™ injection for BPH

FDA submission commenced (IND #61337)
BTX-A injection into the prostate

- SD rat
- BTX-A injection
- Harvest at 1st and 2nd week

- inducing apoptosis
- inhibiting proliferation
- down-regulating α1A ARs

**BTX-A may potentially be the drug that has dual actions on the static and dynamic components of BPH.**

Chuang YC et al. J Urol. 2006
## BTX Injection: Clinical Results

<table>
<thead>
<tr>
<th>Author</th>
<th>No. BPH pt</th>
<th>Dose</th>
<th>Efficacy</th>
<th>A.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria G (2003)</td>
<td>RCT 30 pts</td>
<td>BTA 200U</td>
<td>Sx score 65% ↓ PSA 51% ↓</td>
<td>None</td>
</tr>
<tr>
<td>Kuo HC (2005)</td>
<td>Prospective 10 hi-risk pts w UR</td>
<td>BTA 200U</td>
<td>8 excellent; 2 improved (Pvoiding, PVR, Vol, Qmax)</td>
<td>None</td>
</tr>
<tr>
<td>Chuang YC (2005)</td>
<td>16 pts (small prostate)</td>
<td>BTA 100U</td>
<td>All pts improved (Vol, SS/QoL, Qmax)</td>
<td>None</td>
</tr>
<tr>
<td>Chuang YC (2006)</td>
<td>8 pts</td>
<td>BTA 200U</td>
<td>All pts improved (Vol, SS/QoL)</td>
<td></td>
</tr>
<tr>
<td>Chuang YC (2006a)</td>
<td>41 pts</td>
<td>BTA 100U (n=21); 200U (n=20)</td>
<td>75.6% pts improves 58.3% pts effective&gt;1yr</td>
<td>None</td>
</tr>
</tbody>
</table>
BTX Injection: Issues to be solved

- Detailed mechanism of action?
- No. of injections?
- Injection route?
- Optimal dose?
**Conclusions**

- A-AR antagonist remains to be a mainstay in the pharmacotherapy for BPH.
- Newer α-AR subtype antagonists are being developed.
- Extensive basic research on the AR subtypes and the mechanism of action is needed.
- Intraprostatic BTX injection may be used in a selected group of patients.