HYPOTHESIS / AIMS OF STUDY

Alpha1-adrenergic blockers are considered the most effective monotherapy for lower urinary tract symptoms (LUTS) suggestive of BPH and phosphodiesterase 5 inhibitors are the first line treatment of erectile dysfunction (ED). LUTS and ED are highly prevalent in aging men and are strongly linked, independently of age. Recently, it has been shown that tadalafil could improve LUTS. Furthermore, a recent placebo-controlled study showed no clinically relevant hemodynamic interaction between alfuzosin and tadalafil. We aimed to evaluate the effect of alfuzosin, tadalafil or a combination of both on human prostatic tissue.

STUDY DESIGN, MATERIALS AND METHODS

Prostatic tissue were obtained from 7 patients undergoing cystoprostatectomy for infiltrating bladder cancer. Prostatic strips were mounted isometrically in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95% O2 and 5% CO2, pH 7.4. Following an equilibration period, concentration-response curves (CRC) to norepinephrine (NE) were performed from 10^-8 to 10^-4M. Then following a 20 min incubation period with either vehicle, or tadalafil (10^-5M), or alfuzosin (3.10^-8M) or a combination of both compounds, CRC to NE was repeated.

RESULTS

Preincubation of the strips with tadalafil 10^-5M significantly inhibited contractions induced by NE (p<0.05, two-way ANOVA). In presence of tadalafil the maximal effect (Emax) of contraction induced by NE on prostatic strips was reduced to 57.4 ± 2.0% of maximal contraction of first CRC versus 71.4 ± 1.7% in presence of vehicle (p<0.05, one-way ANOVA) and shifted the CRC to NE to the right by 4.8 fold (p<0.05, Student t test). The preincubation with the combination of tadalafil and alfuzosin had a greater relaxant effect on NE-induced contractions compared to alfuzosin alone (tadalafil+alfuzosin versus alfuzosin, p<0.001). Moreover, the CRC to NE in presence of the combination was shifted to the right by 5.6-fold when compared to the CRC performed with tadalafil alone (p<0.01, one-way ANOVA).

INTERPRETATION OF RESULTS

These results support that a combination of tadalafil and alfuzosin could be an effective therapy to treat simultaneously LUTS in patients with BPH and ED as it has been recently suggested in a recent pilot study where the combination of an alpha-blocker and a PDE5 inhibitor was superior to monotherapy in treating LUTS in men with ED.

CONCLUDING MESSAGE

Alfuzosin and tadalafil exert an additive relaxant effect on NE-contracted human prostatic tissue. The value of such a combination therapy in BPH patients with LUTS deserves further investigation in placebo-controlled studies.

(1) Urology 2006, 67, 1199-1204
Combination of alfuzosin and tadalafil exerts an additive relaxant effect on human prostate

Stephanie Oger1, Delphine Behr-Roussel1, Olivier Leco2, Thierry Lebret2, Yves Denoux2, Pierre Denys3, Francois Giuliano4

(1) Pelvipharm, Gif-Sur-Yvette, France. (2) Foch Hospital, Dept. of Urology, Suresnes, France. (3) Raymond Poincare Hospital, Dept. of Neurological Rehabilitation, Garches, France.

This work was supported by sanofi-aventis

INTRODUCTION

- Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are highly prevalent in aging men and are strongly linked, independently of age and cardiovascular comorbidities1.
- Alpha1-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS suggestive of benign prostatic hyperplasia (BPH)2.
- Phosphodiesterase 5 (PDE5) inhibitors such as tadalafil are the first line treatment for ED3.
- There is evidence from three recent phase II double-blind placebo-controlled studies that PDE5 inhibitors including tadalafil significantly improve LUTS/BPH4-6.
- Alpha1-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS suggestive of benign prostatic hyperplasia (BPH)2.
- There is no clinically relevant hemodynamic interaction between alfuzosin 10mg monotherapy to improve both LUTS/BPH and ED6.
- Phosphodiesterase 5 (PDE5) inhibitors such as tadalafil are the first line treatment for ED3.
- There is no clinically relevant hemodynamic interaction between alfuzosin 10mg once daily and tadalafil 20mg once daily.

AIMS OF THE STUDY

- We aimed to evaluate in vitro the effect of alfuzosin, tadalafil or a combination of both drugs on human prostatic tissue.
- In vitro contractile experiments

Effect of tadalafil on norepinephrine-induced contractions of human prostatic strips

<table>
<thead>
<tr>
<th>pD2</th>
<th>Emax (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>vehicle</td>
<td>5.65 ± 0.07</td>
<td>65.43 ± 3.01</td>
</tr>
<tr>
<td>tadalafil 10^-5M</td>
<td>5.72 ± 0.16</td>
<td>68.42 ± 4.62</td>
</tr>
</tbody>
</table>

- Alfuzosin and tadalafil exert in vitro an additive inhibitory effect on norepinephrine-contracted human prostatic tissue.
- Combination of alfuzosin and tadalafil exerts an additive relaxant effect on human prostate.
- These results support that a combination of tadalafil and alfuzosin could be an effective therapy to treat LUTS associated with BPH.
- The value of combining both drugs in BPH patients with LUTS deserves further investigation in placebo-controlled studies.

RESULTS

- The combination of tadalafil (10^-5M) and alfuzosin (3.10^-8M) exerted a greater inhibitory effect on NE-induced contractions of human prostatic strips compared to tadalafil or alfuzosin alone.
- The effect of the high dose combination was greater than the low dose combination.

CONCLUSIONS

- Alfuzosin and tadalafil exert in vitro an additive inhibitory effect on norepinephrine-contracted human prostatic tissue.
- These results support that a combination of tadalafil and alfuzosin could be an effective therapy to treat LUTS associated with BPH.
- The value of combining both drugs in BPH patients with LUTS deserves further investigation in placebo-controlled studies.