

ICS 2007 ABSTRACT

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 tadalafil¹. 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 (E_{max}) 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). As expected, preincubation with alfuzosin 3.10⁻⁸M inhibited contractions induced by NE (p<0.001, two-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 α-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

ICS 2007

37th Annual Meeting of the International Continence Society
Rotterdam, The Netherlands. 20th - 24th August 2007

Combination of alfuzosin and tadalafil exerts an additive relaxant effect on human prostate

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PELVI PHARM

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.
- A pilot clinical study also indicates that alfuzosin 10mg once daily in combination with a PDE5 inhibitor (sildenafil 25mg once daily) may be superior to monotherapy to improve both LUTS/BPH and ED⁷.
- There is no clinically relevant hemodynamic interaction between alfuzosin 10mg once daily and tadalafil 20mg once daily⁷.

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.

MATERIALS & METHODS

Human prostatic strip preparation

Human prostate samples were obtained from 9 patients undergoing cystoprostatectomy for infiltrating bladder cancer. Prostatic strips were suspended in 5 ml organ chambers filled with Krebs-HEPES buffer containing 118 mM NaCl; 4.7 mM KCl; 1.2 mM MgSO₄; 1.2 mM KH₂PO₄; 2.5 mM CaCl₂; 4.2 mM NaHCO₃; 11.1 mM glucose, and 20.8 mM HEPES. Indomethacin (10⁻⁵ M) and dexamethasone (10⁻⁵ M) were also added to the organ bath throughout the experiments to eliminate possible interferences of cyclooxygenase products or induction of NO-synthase. Organ chambers were maintained at 37°C and continuously bubbled with 95% O₂ and 5% CO₂ to maintain a pH at 7.4.



In vitro contractile experiments

The tissue preparations were allowed to equilibrate for 60 minutes, while being washed periodically with fresh Krebs-HEPES buffer. Following the equilibration period, the prostatic tissues were primed by the addition to the organ bath of KCl (90 mM, 10 min), washed, and then primed by the addition of norepinephrine (NE) at 10⁻⁶ M during 5 min. After the priming period, the strips were washed by fresh Krebs-HEPES solution and allowed to re-equilibrate for 20 minutes. Concentration-response curves (CRC) to NE were performed. Then following a 20-min incubation period with either vehicle, tadalafil (10⁻⁶ or 10⁻⁵M), alfuzosin (3.10⁻⁸M) or a combination of tadalafil and alfuzosin (10⁻⁶ + 3.10⁻⁸M or 10⁻⁵ + 3.10⁻⁸M for tadalafil and alfuzosin respectively), CRCs to NE were repeated.

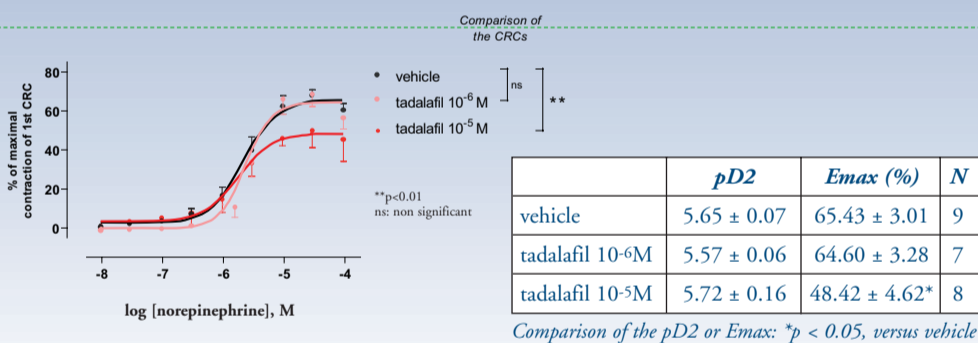
Data Analysis

Results of the second CRC to NE were expressed in percentage of the maximal value obtained during the first CRC. For each CRC in presence of the tested vehicle or compound(s), a pD₂ value (-log concentration of compound that produces 50% reduction of the maximal response) and a mean maximal effect (Emax) were determined using the four-parameter logistic model.

Data were expressed as mean ± SEM for N experiments corresponding to N prostatic samples. Statistical analysis was performed according to the extra sum of squares F test principle with GraphPad Prism® 4.03 software.

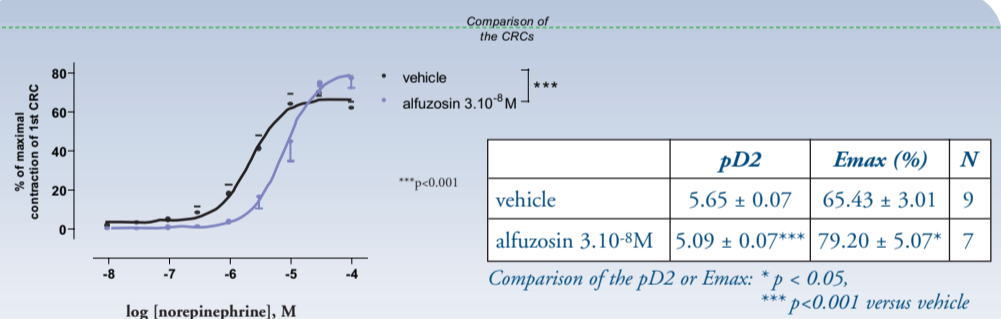
RESULTS

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



- Tadalafil (10⁻⁵M) reduced the maximal effect of NE-induced contractions

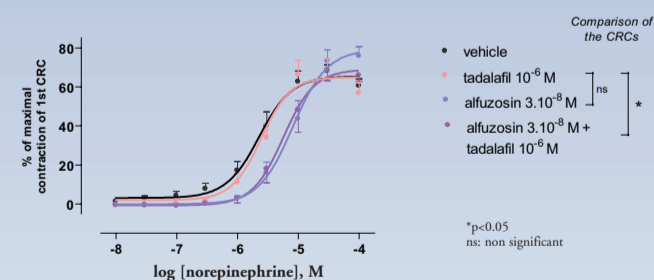
Effect of alfuzosin on norepinephrine-induced contractions of human prostatic strips



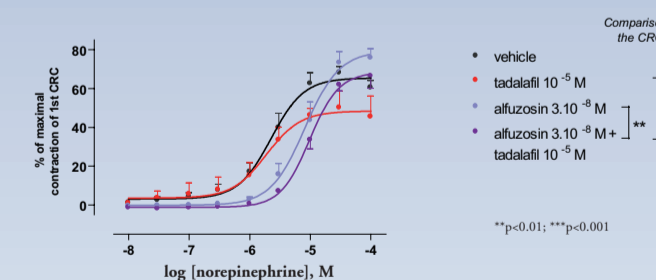
- Alfuzosin significantly shifted to the right the CRC to NE without reducing the maximal effect, in accordance with its competitive α₁- antagonist pharmacological profile

Effect of the combination of tadalafil and alfuzosin on norepinephrine-induced contractions of human prostatic strips

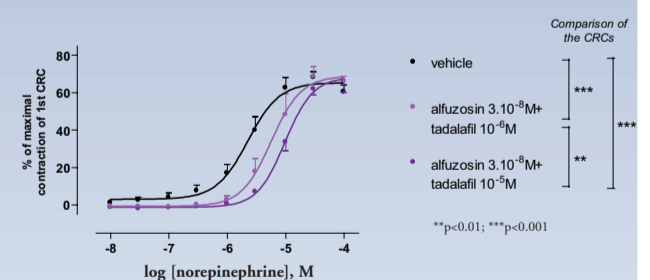
Effect of low dose combination



Effect of high dose combination



Effect of low & high dose combinations



- 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 to 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.