

COMBINATION OF ALFUZOSIN AND TADALAFIL EXERTS ADDITIVE RELAXANT EFFECT ON HUMAN PROSTATE THIS WORK WAS SUPPORTED BY SANOFI-AVENTIS

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 (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). 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.

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HUMAN SUBJECTS: This study did not need ethical approval because Prostate samples are obtained from donors undergoing cystoprostatectomy for bladder cancer. They are collected with patient informed consent. This procedure is sufficient to obtain such human prostate samples in France. but followed the Declaration of Helsinki Informed consent was obtained from the patients.