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

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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 comorbidities.

Alpha-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS suggestive of benign prostatic hyperplasia (BPH).

Phosphodiesterase 5 (PDE5) inhibitors such as tadalafil are the first line treatments for ED.

There is evidence from three recent phase II double-blind placebo-controlled studies that PDE5 inhibitors including tadalafil significantly improve LUTS/BPH.

A pilot clinical study also indicates that alfuzosin 10mg once daily in combination with a PDE5 inhibitor (tadalafil 20mg once daily) may be superior to monotherapy to improve both LUTS/BPH and ED.

There is no clinically relevant hemodynamic interaction between alfuzosin 10mg once daily and tadalafil 20mg once daily.

AIM 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 transrectal ultrasonography for investigating 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, 2.5 mM CaCl2, 2 mM NaHCO3, 11.5 mM glucose, and 20.8 mM HEPES. Ismoton 100 (M) and denatonium (100 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 of the agonist to the organ bath (KCl 90 (60 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.

Data Analysis

Results of the second CRC to NE were expressed in percentage of the maximal value obtained during the first CRC.

Effect of high dose combination

| Vehicle | 5.72 ± 0.16 | 45.82 ± 4.62 |
| Tadalafil 10^-5 M | 5.01 ± 0.07## | 68.32 ± 3.06 |
| Tadalafil 10^-5 M + alfuzosin 3.10^-8 M | 5.24 ± 0.08* | 79.20 ± 5.07 |

## p<0.001 versus vehicle.

Effect of low dose combination

| Vehicle | 5.65 ± 0.07 65.43 ± 3.01 |
| Tadalafil 10^-6 M | 5.09 ± 0.07*** | 79.20 ± 5.07* |
| Tadalafil 10^-5 M | 5.57 ± 0.06 64.60 ± 3.28 |
| Tadalafil 10^-5 M + alfuzosin 3.10^-8 M | 5.01 ± 0.04***## | 68.32 ± 3.06 |

## p<0.001 versus vehicle.

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.