Combination of alfuzosin and tadalafil exerts an additive enhancing effect on norepinephrine-induced relaxation of pre-contracted human detrusor smooth muscle

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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-1 adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS associated with benign prostatic hyperplasia (BPH).
- Phosphodiesterase 5 (PDE5) inhibitors are a first line treatment for erectile dysfunction (ED).
- Recent clinical trials have shown that PDE5 inhibitors (sildenafil, tadalafil, vardenafil) could improve not only ED but also obstructive and irritative LUTS associated with BPH.
- Interestingly, this beneficial effect on LUTS is not associated with an increased peak flow rate suggesting an extraprostatic mode of action.
- Alfuzosin (10-5M) enhances the relaxant effect of NE on carbachol pre-contracted detrusor strips.
- Tadalafil from 10-6 to 10-5M does not enhance NE-induced relaxation of carbachol pre-contracted detrusor strips.

AIM OF THE STUDY
- We evaluated in vitro the effect of alfuzosin, tadalafil or a combination of both drugs on norepinephrine (NE)-induced relaxation of pre-contracted human detrusor strips.

MATERIALS & METHODS

Human detrusor strip preparation
Bladders samples were obtained from 7 patients undergoing cystectomy for bladder cancer with no history of bladder dysfunction. Sensal and mucosal layers were removed from bladder samples, and detrusor strips were mounted in 5 ml organ baths filled with Krebs-HEPES buffer maintained at 37°C and continuously bubbled with 95%O2-5%CO2. The strips were connected to force transducers for isometric tension recordings (Pioden Controls Ltd, UK). Following amplification, the tension changes were computerized using Chart™ 6 software (AD Instruments Ltd).

In vitro contractile experiments
Strips were exposed to carbachol (10-4M, 10 minutes) followed by NE (10-3M, 10 minutes) to evaluate their contractile and relaxant capacity. Then strips were incubated for 20-minute period with alfuzosin (at two different concentrations: 10-6 and 10-5M) or tadalafil at two different concentrations: 10-6 and 10-5M) or two combinations of both compounds (alfuzosin 10-5M + tadalafil 10-6M and alfuzosin 10-5M + tadalafil 10-6M) / vehicle + CRC NE

RESULTS

Effect of alfuzosin on the relaxation induced by NE on carbachol pre-contracted human detrusor strips

Effect of low dose combination

Effect of low & high dose combinations

Effect of high dose combination

Effect of low dose combination

Effect of high dose combination

Comparison between the pD2 or Emax: *p<0.05 versus vehicle
Comparison between the pD2 or Emax: #p<0.05 versus tadalafil 10-6M + CRC NE
Comparison between the pD2 or Emax: **p<0.01 versus tadalafil 10-6M + CRC NE

Effect of low & high dose combinations

Comparison between the pD2 or Emax: ***p<0.001 versus vehicle

CONCLUSIONS
- Tadalafil from 10-6 to 10-5M does not enhance NE-induced relaxation of carbachol pre-contracted detrusor strips.
- Alfuzosin enhances the relaxant effect of NE on carbachol pre-contracted detrusor strips.
- These experiments provide experimental support for the clinical investigation of the combination of alpha-1-blockers and PDE5 inhibitors in the treatment of LUTS associated with BPH and possibly overactive bladder.