Combination of alfuzosin and tadalafil exerts an additive relaxing effect on precontracted human corpus cavernosum

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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 comorbidities[1].
- $Alpha_1$-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS suggestive of benign prostatic hyperplasia (BPH)[2].
- Phophodiesterase 5 (PDE5) inhibitors (tadalafil, sildenafil, vardenafil) are the first line treatment of erectile dysfunction (ED)[3]. However, there is still an unmet need for the management of men who do not respond to PDE5 inhibitors such as diabetic or neurologically impaired patients.
- It has been reported that 71% of non responders to tadalafil monotherapy (20 mg on demand) have an improvement of ED when alfuzosin 10mg once daily (OD) is combined[4]. Moreover, a recent pilot study suggested that daily administration of both alfuzosin 10 mg and sildenafil 25 mg for 12 weeks in men with previously untreated ED is more effective than sildenafil alone to enhance erectile function[5].
- Alfuzosin has no deleterious effect on erectile and ejaculatory function and shows no clinically relevant hemodynamic interaction with tadalafil at the maximum prescribed dose (20 mg)[6-7].

AIM OF THE STUDY

- **We evaluated in vitro the effect of alfuzosin, tadalafil or the combination of both drugs on precontracted human cavernosal strips.**

MATERIALS & METHODS

Human cavernosal strip preparation

Human cavernosal tissues were obtained from 10 patients undergoing penile surgery for penile implant as treatment of erectile dysfunction, penile congenital curvature or for Peyronie's disease. Cavernosal 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 $CaCl_2$; 4.2 mM NaHCO3; 11.1 mM glucose, and 20.8 mM HEPES. 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

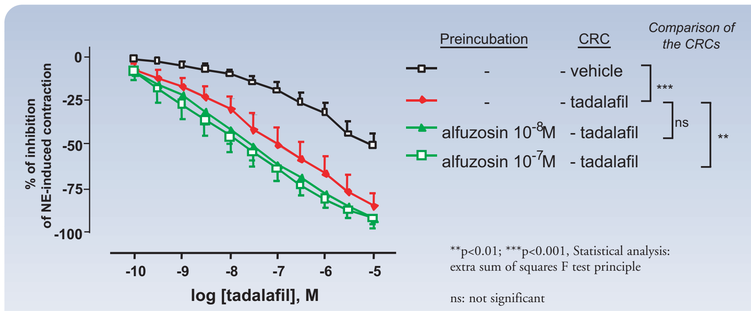
(1) Strips were incubated with either alfuzosin or vehicle during 20 min. Concentration-response curves (CRC) for tadalafil or vehicle were then constructed on norepinephrine (NE) (1 to 10 µM)-induced precontracted human cavernosal strips. (2) Vehicle or tadalafil or alfuzosin or a combination of both were added for 20 min and frequency response curves (FRC) to electrical field stimulation (EFS) were performed on each strip. (3) Guanethidine (5 mM) and atropine (1 mM) were added to Krebs-Hepes buffer. Strips were precontracted with NE (1 to 10 µM) and submitted to EFS (20 Hz- 300mA-1 ms-10s). Following a 20-min incubation period with either alfuzosin, or tadalafil or a combination of both, NE-precontraction of the strips followed by EFS were repeated.

Data Analysis

The relaxation in response to tadalafil or vehicle was expressed in percentage of inhibition of NE-induced contraction. The contractile responses induced by EFS were expressed as a percentage of the priming contraction to EFS (32 Hz-300 mA-1ms-10s). Relaxant responses to EFS were expressed in percentage of increase in amplitude or duration of EFS-induced relaxation of the first relaxation response obtained before the incubation with alfuzosin, tadalafil or a combination of both. For each CRC performed for tadalafil, a pD_2 value (-log [EC50] where EC50 was the concentration of drug that produced 50 % of the maximum effect) and a maximal effect value (Emax, maximum response that can be produced by the highest concentration of the drug used) were determined. Data were expressed as mean ± SEM for N experiments corresponding to N prostatic samples. Statistical analysis was performed with GraphPad Prism® 4.03 software.

RESULTS

Effect of alfuzosin on the relaxation induced by tadalafil on NE-induced cavernosal contraction



**p<0.01; ***p<0.001, Statistical analysis: extra sum of squares F test principle

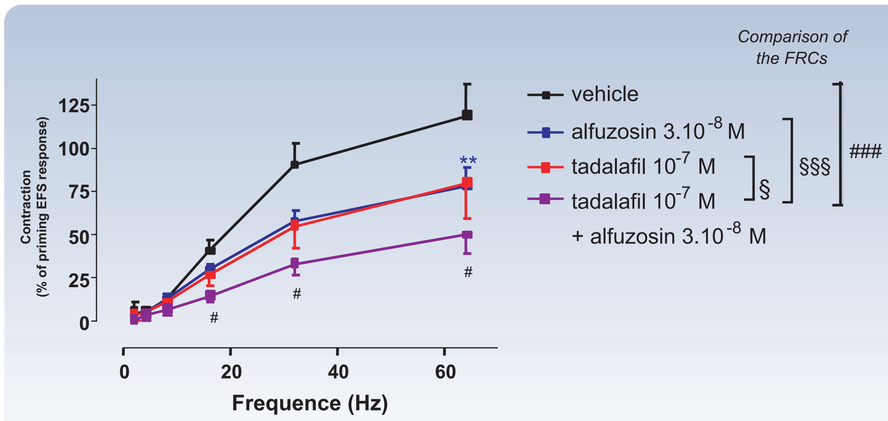
ns: not significant

- Tadalafil from 10^{-10} to 10^{-5}M induces a significant concentration-dependent relaxation of NE-induced contraction of human cavernosal strips when compared to vehicle.
- This effect is significantly enhanced by the presence in the organ bath of alfuzosin at 10^{-7}M

Pretreatment	None (n=10)	Alfuzosin 10^{-8}M(n=7)	Alfuzosin 10^{-7}M(n=5)
Emax (%)	-75.0 ± 4.2	-81.6 ± 3.9	-83.4 ± 3.7
pD2	7.2 ± 0.1	7.5 ± 0.1	7.6 ± 0.1

No statistical difference between groups for Emax and pD2

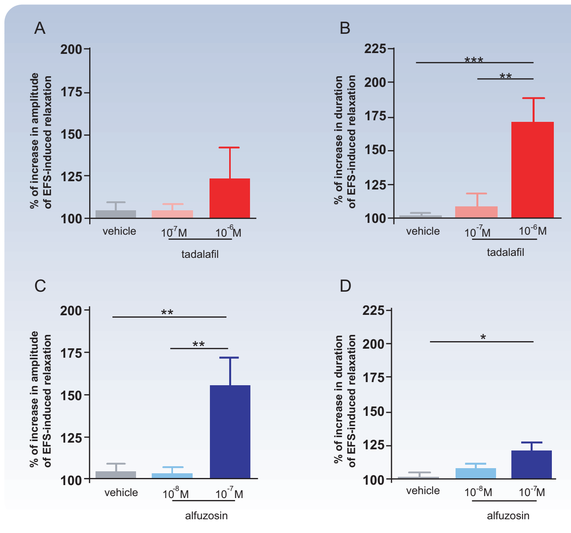
Effect of tadalafil, alfuzosin or a combination of both on EFS-induced cavernosal contraction



$p<0.05, $$$p<0.001, two-way ANOVA followed by followed by Bonferroni posttest:*p<0.05, **p<0.01. #p<0.05, ###p<0.001, two-way ANOVA with interaction followed by a modified Student t-test with the Bonferroni adjustment for multiple comparisons.

- The combination of tadalafil and alfuzosin is more efficient to inhibit human cavernosal contraction induced by increasing EFS frequency than each compound alone.

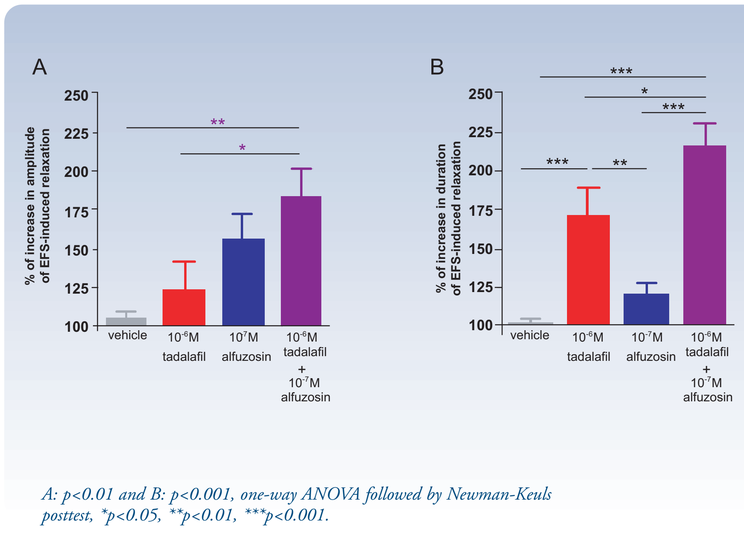
Effect of alfuzosin or tadalafil on the nitrergic non-adrenergic non-cholinergic (NANC) relaxation induced by EFS on NE-precontracted cavernosal strips



- The pre-treatment of strips with tadalafil 10^{-7}M has no effect on the amplitude of nitrergic NANC relaxation induced by EFS while tadalafil 10^{-6}M tends to enhance the amplitude of relaxation although this effect is not significant. In contrast, tadalafil increases in a dose dependent manner the duration of the relaxation induced by EFS.
- The pre-treatment of strips with alfuzosin at 10^{-7}M significantly increases the amplitude and, to a lesser extent, the duration of EFS-induced relaxation. Alfuzosin at 10^{-8}M does not modify the relaxant response induced by EFS.

*A: non significant, B: p<0.001, C: p<0.01 and D: p<0.05 one-way ANOVA followed by Newman-Keuls posttest, *p<0.05, **p<0.01, ***p<0.001.*

Effect of the combination of alfuzosin & tadalafil on the nitrergic non-adrenergic non-cholinergic relaxation induced by EFS on NE-precontracted cavernosal strips



- The combination of tadalafil 10^{-6}M and alfuzosin 10^{-8}M, significantly increases the amplitude of the relaxation and its effect is significantly greater than tadalafil 10^{-6}M alone suggesting an additive effect of the combination.
- In addition, the combination of tadalafil 10^{-6}M and alfuzosin 10^{-7}M also prolongs the relaxation to EFS to a greater extent than tadalafil 10^{-6}M or alfuzosin 10^{-7}M alone.

*A: p<0.01 and B: p<0.001, one-way ANOVA followed by Newman-Keuls posttest, *p<0.05, **p<0.01, ***p<0.001.*

CONCLUSIONS

- **In vitro, the combination of alfuzosin and tadalafil is more efficient than each compound alone to relax the adrenergic tone or to enhance nitrergic relaxation.**
- **As a considerable population of patients with erectile dysfunction do not respond to PDE5 inhibitors, such a combination therapy deserves further investigation in well-designed placebo-controlled studies in patients complaining of erectile dysfunction and not responding to tadalafil alone.**

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