

Tadalafil exerts an additive effect on alfuzosin-induced relaxation in pre-contracted human isolated prostatic adenoma

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INTRODUCTION

- Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are highly prevalent in aging men with benign prostatic hyperplasia (BPH) and are strongly linked, independently of age and cardiovascular comorbidities¹⁻².
- Alpha₁-blockers (alfuzosin, doxazosin, tamsulosin, terazosin) are considered the most effective monotherapy for LUTS associated with BPH³. They act by relaxing smooth muscle tone in the prostate which is predominantly mediated by α₁-adrenoceptors.
- Phosphodiesterase (PDE) 5 inhibitors (sildenafil, tadalafil, vardenafil) are the standard treatment for ED⁴. Placebo-controlled trials have shown that they improve LUTS associated with BPH⁵⁻⁷ and this effect is biologically plausible. Nitric oxide (NO) levels are reduced in transition zone of human adenoma compared to normal prostate². NO has a direct relaxant effect on human isolated prostate⁸. A fall in NO levels could thus contribute to increase prostatic smooth muscle tone in BPH patients. Moreover, PDE5 isoenzymes have been identified in transitional zone of human prostate, along with PDE4 and PDE11².
- Together, these findings suggest that the co-administration of an α₁-blocker and a PDE-5 inhibitor in men with LUTS associated with BPH may be of benefit by combining the effect of each drug alone. Indeed, the combination of alfuzosin and tadalafil shows an additive relaxant effect on human non adenomatous prostate tissue⁹ and corpus cavernosum in vitro¹⁰. A recent pilot study also suggested that daily intake of alfuzosin 10 mg and sildenafil 25 mg for 12 weeks was safe and more effective than monotherapy to improve LUTS and sexual dysfunction in men with BPH¹¹.

AIM OF THE STUDY

- This study was aimed at determining whether the combination of alfuzosin and tadalafil is more effective than each drug alone in relaxing prostatic muscle strips obtained from the transitional zone of men requiring surgery for BPH.

MATERIAL & METHODS

- Human prostate specimens (transitional zone) were obtained from 11 men (mean age 68.8±3.2 years) undergoing transvesical prostatectomy or transurethral resection of the prostate for BPH in 2 French Urology departments. Institutional approvals for use and shipment of human tissues were obtained, and all patients gave written informed consent. Tissues were placed in a cold storage solution and transported to the laboratory, immediately after surgery, in a container at 4°C. Upon receipt, tissues were stored at 4°C until the start of the experiment.
- Strips were connected to tension transducers in organ baths containing Krebs solution. Prostatic strips were allowed to equilibrate for 1 hour at a preload tension of 1.5 g, during which tissues were washed with Krebs Henseleit solution every 15 min. At the end of the equilibration time, strips were exposed to 30 μM norepinephrine (NE) to measure their viability. Strips with contractile response below 0.3 g were discarded.
- After washout and 1-hour re-equilibration, solvent (dimethylsulfoxide, DMSO) or cumulative concentrations (0.01 to 10 μM) of alfuzosin, tadalafil or alfuzosin+tadalafil were tested on the plateau of contractions induced by A-61603 (0.1 μM), a selective α₁-adrenoceptor agonist. For a given patient, alfuzosin, tadalafil or alfuzosin + tadalafil were tested in separate strips. Each concentration was added after having obtained a clear plateau of relaxation. DMSO concentration in organ bath ranged from 0.001% to 1% when testing alfuzosin or tadalafil alone (250 μl solvent for each compound) and from 0.002% to 2% when testing alfuzosin+tadalafil (250 μl for alfuzosin + 250 μl for tadalafil).
- Relaxant effects were expressed as the percentage inhibition of the plateau of contractions to A-61603, measured just before testing the relaxant compounds.
- Between group comparisons were done on measures obtained in the same patient. Comparisons were performed by a Winer analysis followed by Student-Newman-Keuls test.

CONCLUSIONS

- In human isolated prostatic adenoma, the combination of alfuzosin and tadalafil shows a greater relaxant effect than alfuzosin alone.
- The clinical relevance of this finding for treating LUTS associated with BPH needs to be confirmed in placebo-controlled clinical studies.

RESULTS

Figure 1A: relaxant effect of tadalafil and DMSO in human isolated prostatic adenoma

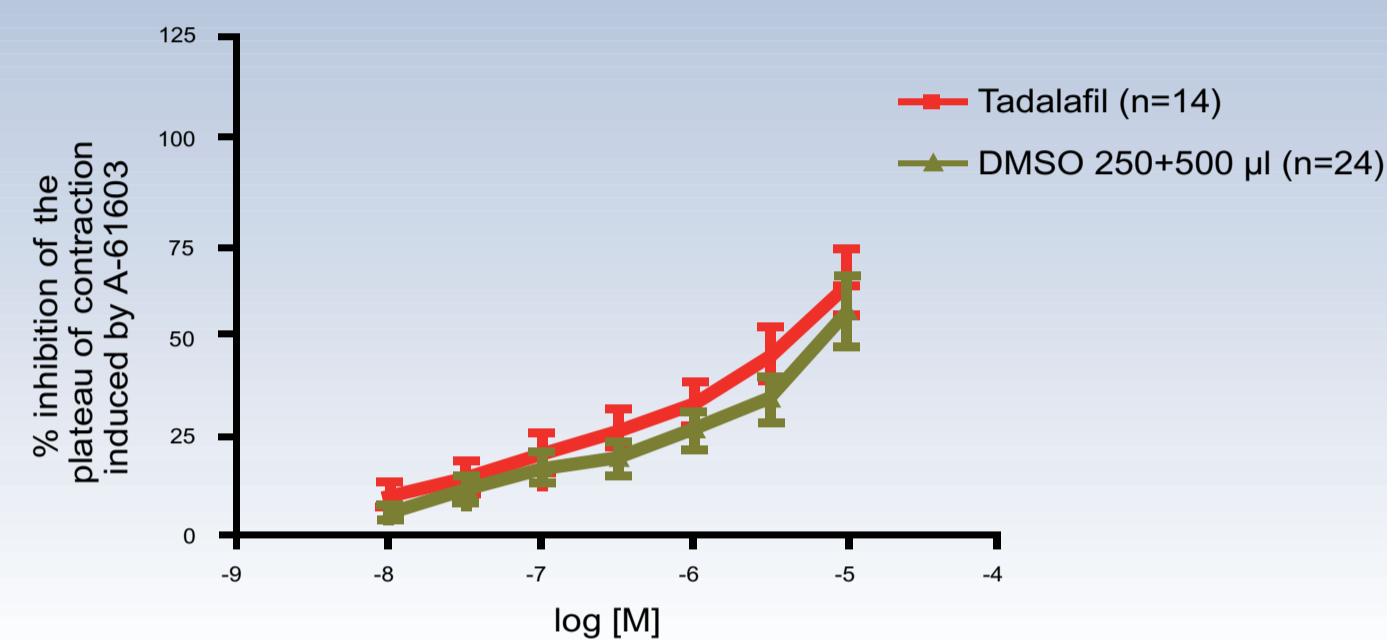
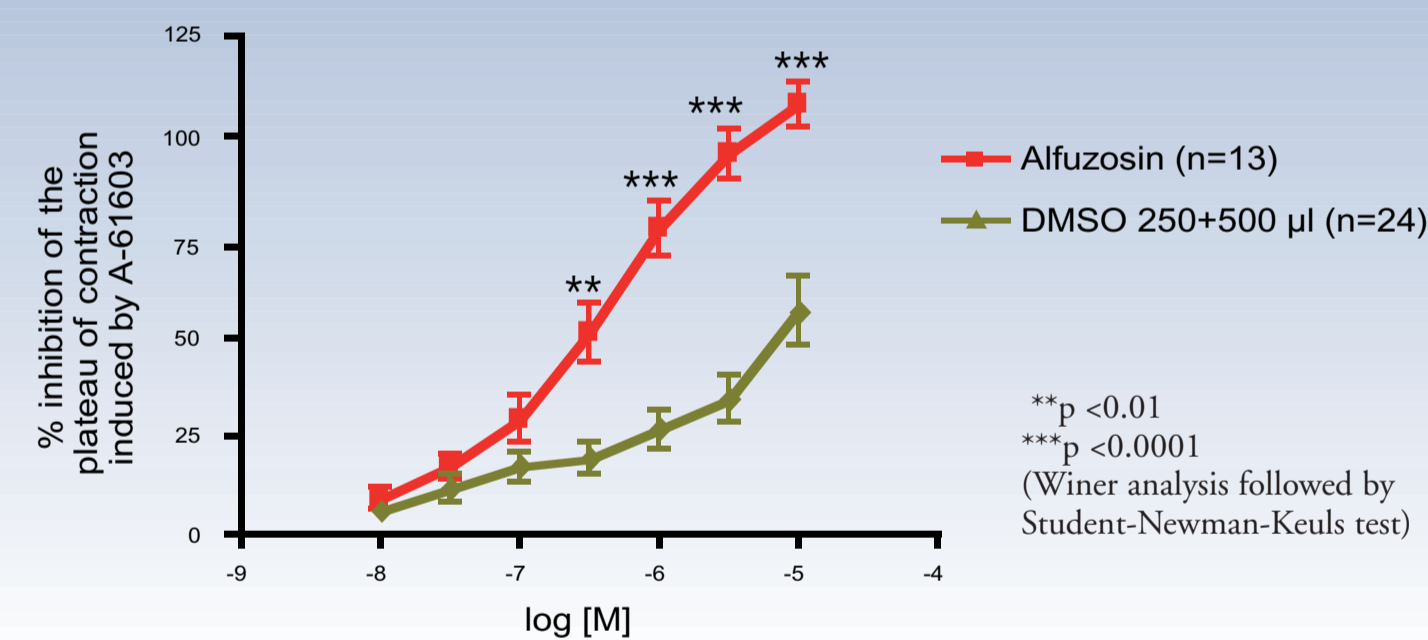


Figure 1B: relaxant effect of alfuzosin and DMSO in human isolated prostatic adenoma



- A-61603 (0.1 μM) induced a stable and sustained contraction of prostatic strips. Mean plateau of contractions value for strips exposed to alfuzosin+tadalafil (1.00±0.15 g, n=14) did not significantly differ from those exposed to tadalafil alone (1.11±0.24 g, n=14), alfuzosin alone (1.45±0.28 g, n=13), DMSO at 250 μl (1.16±0.22 g, n=14) and DMSO at 500 μl (0.97±0.21 g, n=10). Maximal relaxant effects induced by DMSO 250 μl (48.1±8.9%, n=14) and DMSO 500 μl (66.5±17.1%, n=10) were not significantly different, allowing to pool both groups.
- Tadalafil alone (n=14) induced a mild relaxation of the plateau of contraction which was not significantly different from DMSO (Figure 1A).
- Alfuzosin alone (n=13) totally abolished, in a concentration-dependent manner, the plateau of contraction induced by A-61603 (Figure 1B). The difference versus DMSO was significant (p<0.01 to <0.0001) for alfuzosin concentrations between 0.3 and 10 μM.

Figure 2A: relaxant effect of tadalafil and the combination of alfuzosin and tadalafil in human isolated prostatic adenoma

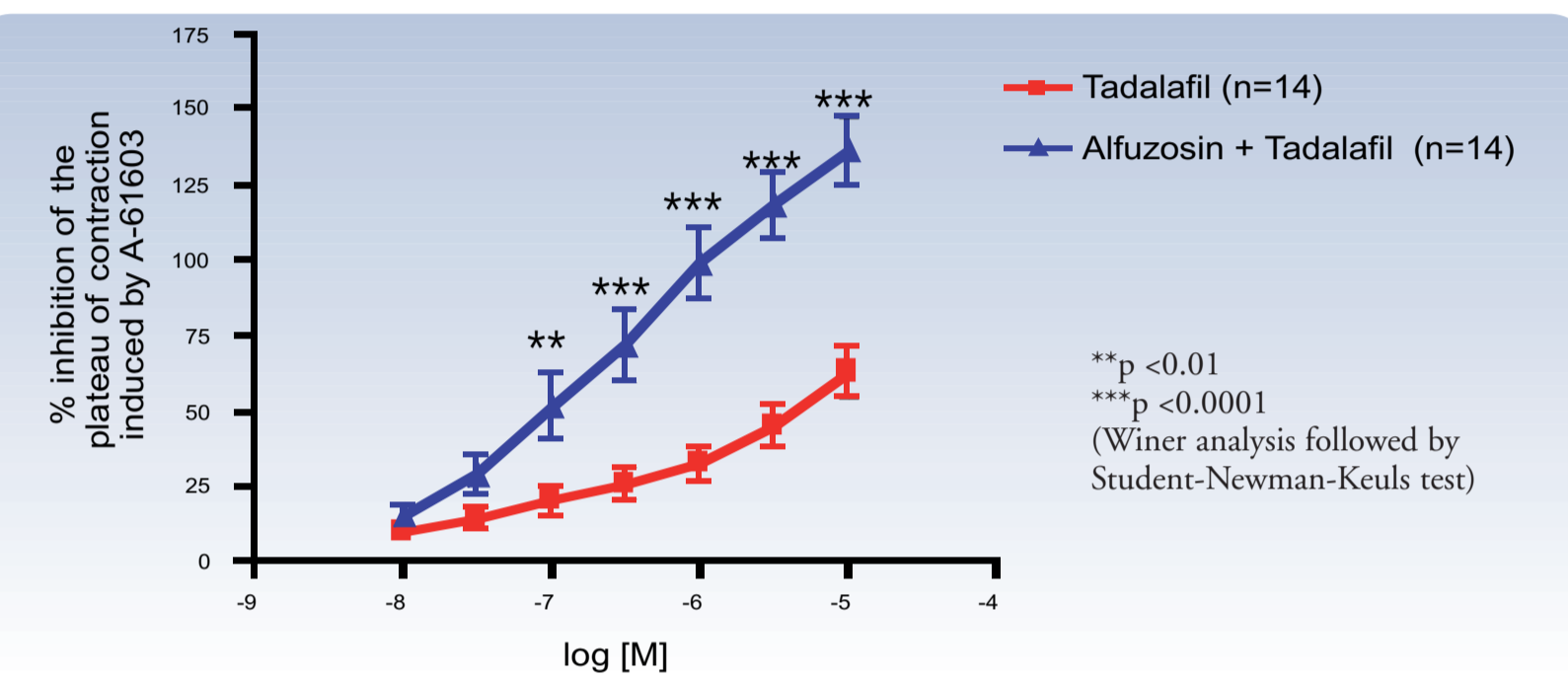
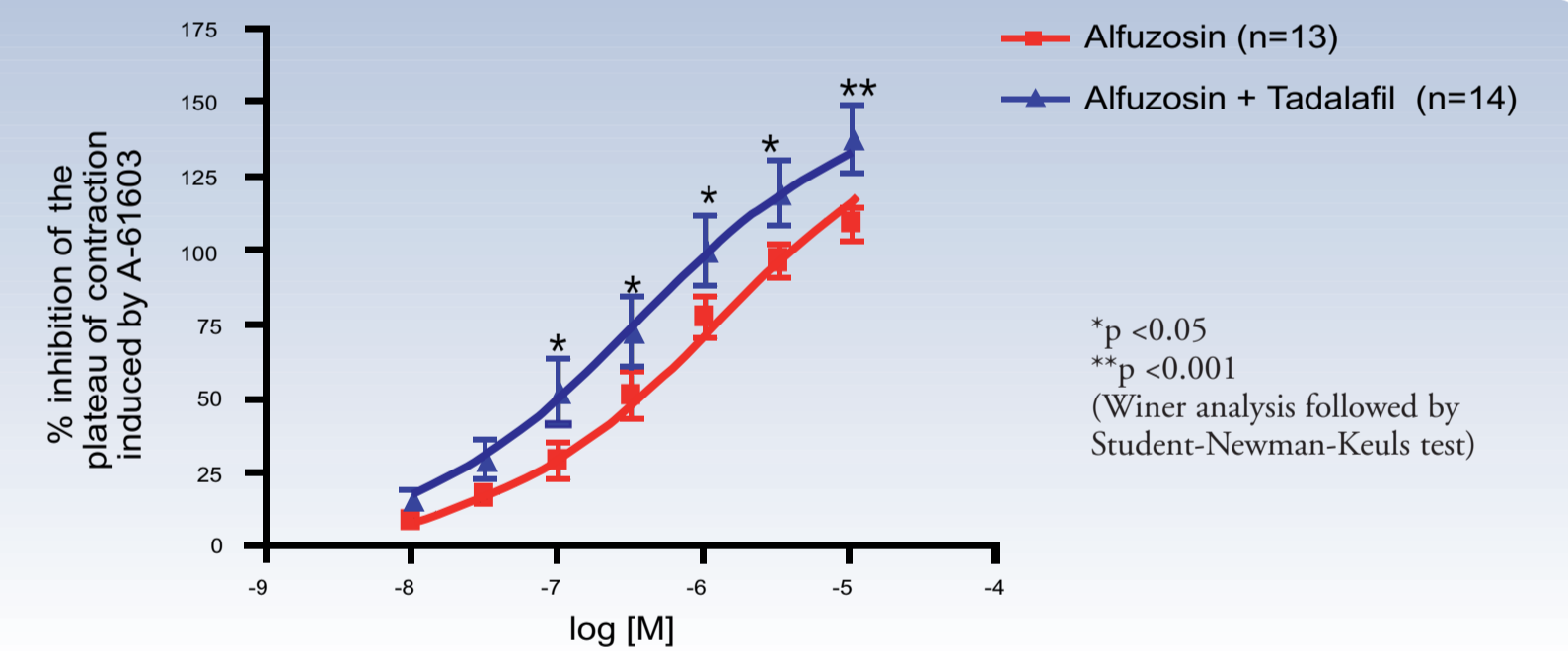


Figure 2B: relaxant effect of alfuzosin and the combination of alfuzosin and tadalafil in human isolated prostatic adenoma



- Alfuzosin+tadalafil (n=14) induced a concentration-dependent relaxation of the plateau of contraction which was significantly greater than alfuzosin alone (p<0.05 to <0.01) and tadalafil alone (p<0.01 to p<0.001) for concentrations between 0.1 and 10 μM (Figure 2A and 2B). The pIC₅₀ value for alfuzosin alone was 5.92±0.23 compared to 6.47±0.24 for the combination of alfuzosin+tadalafil (p< 0.0001).

Comparison with therapeutic concentrations used in humans

- Concentrations used in this experimental model are in agreement with therapeutic concentrations used in humans. In patients, alfuzosin at 10 mg once daily (recommended dose for treating LUTS), produces a maximal plasma concentration (C_{max}) corresponding to a concentration of 0.094 μM in the prostatic tissue¹². This is closed to the concentration (0.1 μM) showing a significant interaction with tadalafil in our experiment. On the other hand, tadalafil at 20 mg once daily (highest recommended dose for treating ED) produces a C_{max} corresponding to a concentration of 1 μM¹³. This is in the range of concentrations tested in our model where potentiation of alfuzosin (0.1 μM) by tadalafil occurred for concentrations as low as 0.1 μM.

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