SPONTANEOUS CONTRACTIONS IN THE TRANSITION ZONE OF PROSTATES FROM MEN WITH BENIGN PROSTATIC HYPERPLASIA OR ENLARGEMENT ARE SIGNIFICALLY REDUCED BY COMBINATION THERAPY

Hypothesis / aims of study
There is ample evidence to suggest that patients treated with low dose PDE-5 inhibitors have an improvement in their lower urinary tract symptoms (LUTS) secondary to prostate enlargement or benign prostatic hyperplasia (BPH); however, the precise mechanism by which PDE-5 inhibitors exert their effects is not known. The aim of this study was to examine the direct effect of a clinically used PDE5 inhibitor, sildenafil, compared to an existing well established treatment for BPH, the \( \alpha_1 \) antagonist tamsulosin, in a novel model of human prostatic contractility.

Study design, materials and methods
Transition zone (TZ) tissue (10mm X 15mm) from the prostate gland was obtained from consenting patients undergoing transurethral resection of prostate or radical prostatectomy. Transition zone tissue was placed into ice-cold RPMI medium supplemented with 5% fetal calf serum and antibiotics (penicillin at 300 units/ml, streptomycin at 300 \( \mu \)g/ml and amphotericin at 1 \( \mu \)g/ml). Contractile recordings were made from prostatic preparations (5mm X 10mm) using standard tension recording techniques as we have previously described. A paired Student’s t-test was used to test for statistical significance (\( P < 0.05 \)).

Results
All specimens contracted spontaneously at a frequency of 1.9 +/- 0.2 contractions per minute; the average duration of each contraction was 13.1 +/- 1.6 seconds. In the TZ of the human prostate, the amplitude of the spontaneous contractions was 0.23 +/- 0.02 N/g (n=22). Sildenafil (10\( \mu \)M) reduced the frequency (by ~40%) and amplitude (by ~27%), of spontaneous contractions recorded in the TZ of the human prostate gland (n=8) (\( P < 0.05 \)). Tamsulosin (0.1nM) reduced the amplitude (by ~27%), but not the frequency of spontaneous contractions recorded in the TZ of the human prostate gland (n=9) (\( P < 0.05 \)). The combination of tamsulosin following sildenafil resulted in a reduction in amplitude by 87% and frequency by 87% (n=4) (\( P < 0.01 \)). The combination of sildenafil following tamsulosin resulted in a reduction in amplitude and frequency by 70% and 65%, respectively (n=6) (\( P < 0.05 \)). The non-specific \( \alpha_1 \) antagonist, 1\( \mu \)M prazosin, had no significant effects on the spontaneous contractions (n=5) (\( P > 0.05 \)).

Interpretation of results
Using this model of human prostatic smooth muscle tone, we have demonstrated that the \( \alpha_1 \) adrenoceptor antagonist tamsulosin and the PDE-5 inhibitor sildenafil directly reduce the spontaneous contractility of the transition zone of the human prostate gland. Our results provide: 1) further validation for the use of PDE-5 inhibitors in the treatment of lower urinary tract symptoms associated with BPH, and 2) proof of mechanism data to support the use of combination therapy utilising \( \alpha_1 \) antagonists with PDE-5 inhibitors.

Concluding message
The potential to use PDE-5 inhibitors, in combination with lower doses of ‘uroselective’ \( \alpha_1 \) antagonists such tamsulosin may prove to be a better strategy than current treatment regimens, especially in patients with comorbidities.

Disclosures
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