

## MECHANISTIC EVIDENCE TO SUPPORT THE USE OF COMBINATION THERAPY TO BETTER MANAGE THE TREATMENT OF LUTS ASSOCIATED WITH BPH

### Hypothesis / aims of study

There is ample clinical and experimental evidence to suggest that monotherapy, using phosphodiesterase (PDE) 5 inhibitors or selective  $\alpha$ -blockers, ameliorates the lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) by reducing prostatic smooth muscle tone. In this study, we provide mechanistic evidence that treatment strategies utilising a combination of phosphodiesterase 5 inhibitors and selective  $\alpha$ -blockers may be more efficacious than either drug alone, in the management of LUTS associated with BPH.

### Study design, materials and methods

Transition zone (TZ) tissue (10mm X 15mm) from the prostate gland was obtained from consenting patients undergoing radical prostatectomy. 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

Robust spontaneous, myogenic contractions were recorded in all preparations obtained from the TZ of the prostate gland. After pre-treatment with tamsulosin (0.1nM) for 30 minutes, sildenafil (10 $\mu$ M) further reduced the amplitude of the spontaneous prostatic contractions by 48% and frequency of spontaneous contractions by 33%. The combination of sildenafil (10 $\mu$ M) after the addition of tamsulosin (0.1nM) resulted in a significant overall reduction of amplitude by 70% (0.07 +/- 0.03 N/g) and the frequency of spontaneous contractions by 65% (0.55 +/- 0.33 min<sup>-1</sup>), relative to control (n=6) (Student's paired t-test,  $P < 0.05$ ).

Conversely, after pre-treatment with sildenafil (10 $\mu$ M), tamsulosin (0.1nM) further reduced the amplitude of spontaneous contractions by 84% and frequency of spontaneous contractions by 27%. The combination of tamsulosin (0.1nM) after the addition of sildenafil (10 $\mu$ M) resulted in a significant overall reduction of amplitude by 87% (0.03 +/- 0.03 N/g), relative to control (n=4) (Student's paired t-test,  $P < 0.01$ ) and a significant overall reduction in and the frequency of spontaneous contractions by ~87% (0.64 +/- 0.53 min<sup>-1</sup>), relative to control (n=4) (Student's paired t-test,  $P < 0.01$ ).

### Interpretation of results

The current study supports the notion that sildenafil and tamsulosin have a direct inhibitory effect on human prostatic smooth muscle tone, with the combination of the two drugs having an enhanced effect on human prostatic smooth muscle tone, in comparison to either drug alone.

### Concluding message

Given that LUTS / BPH and erectile dysfunction share common pathophysiology, treatment strategies using combination therapies of PDE5 inhibitors and alpha 1 antagonists may be more efficacious than either drug alone, in the management of BPH in men with or without erectile dysfunction. Further studies are needed to assess long term safety and efficacy.

### Disclosures

**Funding:** NHMRC Clinical Trial: No **Subjects:** HUMAN **Ethics Committee:** Cabrini Human Research Ethics Committee (13-14-04-08), Epworth HealthCare Human Ethics Committee (53611) and Monash University Human Research Ethics Committee (2004/145). **Helsinki:** Yes **Informed Consent:** Yes