Abstract # 1582

Combined effect of a phosphodiesterase 5 inhibitor, udenafil, with an antimuscarinic, oxybutynin on human detrusor relaxation

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OBJECTIVES

- Antimuscarinics are standard therapy for the treatment of overactive bladder (OAB), however their use is not satisfactory since they have a poor tolerability because of their atropinic side effects [1].
- There is emerging evidence that phosphodiesterase 5 (PDE5) inhibitors may have a potential in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Indeed, several randomized placebo controlled trials have recently demonstrated that the three available PDE5 inhibitors (sildenafil [2], vardenafil [3] and tadalafil [4, 5]) improve both voiding (obstructive) and storage (irritative) urinary symptoms.

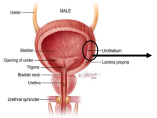
We compared the effects of various PDE5 inhibitors and assessed the potential benefit of a combination of oxybutynin with the most effective PDE5 inhibitor at relaxing human detrusor smooth muscle.

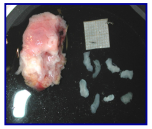
*(1) **Gopal**, et al Obstet Gynecol; 2008;112 (6): 1311-8; **(2) McVary KT**, et al J Urol 2007;177:1071-1077; **(3) Stief CG**, et al Eur Urol 2008;53:1236-1244; **(4) McVary KT**, et al, J Urol 2007;177:1401-1407; **(5) Roehrborn** et al., J Urol 2008; Oct;180(4):1228-34.*

MATERIALS & METHODS

✓ ***Human detrusor strip preparation***

Human bladder samples were obtained from 15 different patients with no known OAB undergoing cystectomy for bladder cancer. Detrusor strips without urothelium were mounted isometrically at a resting tension of 500 mg in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95%O_2-5%CO_2. The strips were connected to force transducers for isometric tension recordings (Pioden Controls Ltd, UK). Following amplification, the tension changes were computerized via MacLab™/8 using Chart™ 5 software (AD Instruments Ltd).





The experiments, collection and use of any tissue or other samples are carried out in accordance with the Research Plan, all relevant laws, regulations and codes of practice, including having obtaining informed consent of patients in writing.

✓ ***In vitro contractile experiments***

The strips were equilibrated for 60 minutes. Then, three set of experiments were performed:

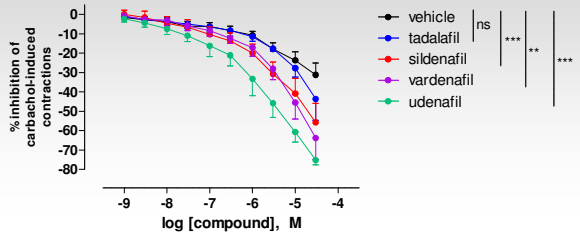
1) Cumulative response curves to sildenafil, vardenafil, tadalafil and udenafil (10^{-9} to 3.10^{-5}M) were performed on precontracted strips with carbachol (10^{-6}M).
2) Strips were preincubated with udenafil (10^{-6}M) or oxybutynin (10^{-8}M) or vehicle, then CRC to oxybutynin or udenafil (from 10^{-9} to 3.10^{-5}M) were constructed on carbachol (10^{-6}M) precontracted human detrusor strips.
3) Frequency response curves (FRC) to electrical field stimulation (EFS) were performed (5, 10, 15, 20, 30, 40 Hz applied every 2 minutes - 0.5 ms pulse duration- 5 s train duration at 300 mA). At the completion of the first FRC, bladder strips were washed and strips were incubated with either vehicle, udenafil (10^{-5}M), oxybutynin (10^{-8}M), or a combination of both, and a second FRC was generated with the same parameters than before.

✓ ***Data Analysis***

For the evaluation of the effect of drugs to inhibit carbachol-induced contractions, relaxations in response to increasing and cumulative concentrations of PDE5 inhibitors or oxybutynin or corresponding concentrations of vehicle are expressed as the percentage of inhibition of the contractile response to carbachol. **For the experiments with electrical field stimulation**, values are expressed in percentage of the maximal contractile response obtained during the first frequency response curve. Data were expressed as mean ± SEM for N experiments corresponding to N = bladder samples obtained, from N different patients. Statistical comparisons of the CRCs were performed with a two-way ANOVA statistic analysis test and Bonferroni's post-test. P values < 0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism® 5.02 software.

RESULTS

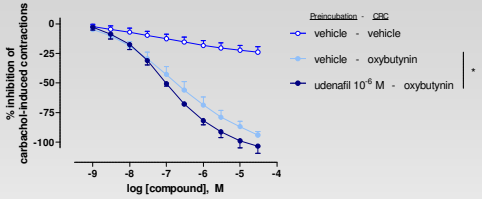
Comparison of the effect of four PDE5 inhibitors on carbachol-induced precontracted human detrusor strips



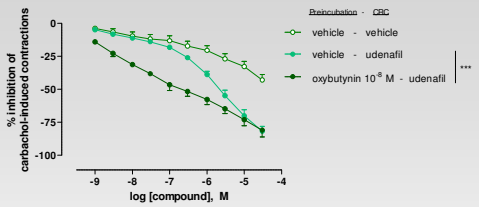
➡ **Udenafil has a greater relaxant effect compared to the other PDE5 inhibitors on carbachol-contracted human bladder strips.**

Combination of udenafil with a muscarinic receptor antagonist: oxybutynin

Evaluation of the enhancing effect of udenafil on oxybutynin-induced relaxations of pre-contracted human detrusor strips

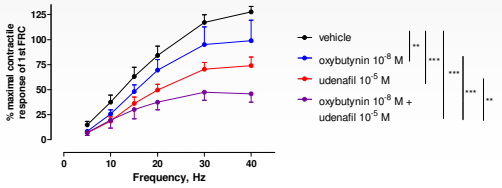


Evaluation of the enhancing effect of oxybutynin on udenafil-induced relaxations of pre-contracted human detrusor strips



➡ **Udenafil at 10^{-6}M enhances the relaxing effect exerted by oxybutynin on precontracted human bladder strips. Conversely, oxybutynin at 10^{-8}M enhances the relaxing effect exerted by udenafil on precontracted human bladder strips**

Evaluation of the effect of udenafil, oxybutynin and a combination of udenafil+oxybutynin on induced contractions on human bladder strips



➡ **The combination of oxybutynin and udenafil exerts a greater inhibitory effect on EFS-induced contractions of human bladder strips than each compound alone**

CONCLUSIONS

- **The relaxant effect of udenafil is superior to the other PDE5 inhibitors on human detrusor smooth muscle.**
- **Its combination to oxybutynin is even better to relax human detrusor, probably due to additive mechanisms of action.**
- **The value of such a combination in OAB patients deserves further investigation in placebo-controlled studies.**