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POTENTIATION OF OXYBUTYNIN-INDUCED HUMAN DETRUSOR RELAXATION BY A PHOSPHODIESTERASE 5 INHIBITOR, UDENAFIL

Hypothesis / aims of study
Recent clinical data indicate that phosphodiesterase (PDE) 5 inhibitors could be effective to improve both voiding and storage lower urinary tract symptoms (LUTS) associated to benign prostatic hyperplasia [1-3] . Anti-muscarinics e.g. oxybutynin represent first line pharmacological treatment for overactive bladder (OAB). However, their use is limited by a mild-to-moderate clinical efficacy and side effects. The aims of this study are (i) to compare the effect of PDE5 inhibitors, sildenafil, vardenafil, tadalafil and udenafil at relaxing human detrusor smooth muscle in order to select the most potent compound in this experimental paradigm and (ii) to assess the potential of a combination of oxybutynin with the most potent PDE5 inhibitor at relaxing human detrusor smooth muscle.
Study design, materials and methods
Human bladder samples were obtained from 15 different patients with no known OAB undergoing cystectomy for bladder cancer. Detrusor strips 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%O2-5%CO2. After an equilibration period, the strips were precontracted with carbachol (10^{-6}M) and then cumulative response curves to sildenafil, vardenafil, tadalafil and udenafil (10^{-9} to 3.10^{-5}M) or vehicle were performed. In a second set of experiments, 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. Finally, strips were incubated with either vehicle, udenafil (10^{-5}M), oxybutynin (10^{-8}M), or a combination of both, and frequency response curves (FRC) to electrical field stimulation (EFS, 0-40 Hz, 0.5 ms, 5s, 300 mA) were performed.
Results
The four PDE5 inhibitors induced a concentration-dependent relaxation of precontracted detrusor strips ($p<0.001$) but with different efficacy. Udenafil was the most efficient compound, inhibiting the contraction by -86.7±4.3% versus -38.3±3.3% for vehicle, followed by sildenafil -67.0±4.3%, vardenafil -62.5±4.3% and tadalafil -52.0±3.7%.
Udenafil at 10^{-6}M enhanced the relaxing effect exerted by oxybutynin on precontracted human bladder strips and conversely, oxybutynin at 10^{-8}M enhanced the relaxing effect exerted by udenafil on precontracted human bladder strips ($p<0.05$ and $p<0.001$, respectively). The combination of oxybutynin and udenafil exerted a greater inhibitory effect on EFS-induced contractions of human bladder strips than each compound alone (udenafil versus udenafil+oxybutynin, $p<0.01$ and oxybutynin versus udenafil+oxybutynin, $p<0.001$).
Interpretation of results
The effect of udenafil was superior to the other PDE5 inhibitors tested at relaxing human detrusor smooth muscle. Other(s) mechanism(s) of action than PDE5 inhibition could be involved in udenafil-induced relaxation of human detrusor smooth muscle. The benefit of the combination of udenafil with oxybutynin to relax human detrusor is probably due to an additive effect of their individual mechanism of action. These data suggest that the clinical use of such combination could be interesting for the treatment of OAB.

Concluding message
Udenafil seems to be more efficient than sildenafil, vardenafil and tadalafil to relax human detrusor smooth muscle. In vitro, the combination of udenafil and oxybutynin is more effective than each compound alone to inhibit carbachol or EFS-induced contractions. The value of such a combination therapy in OAB patients deserves further investigation in placebo-controlled studies.
References
1. McVary, et al J Urol. 2007;177:1401-1407
2. McVary, et al J Urol 2007;177:1071-1077
3. Stief, et al Eur Urol 2008

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Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require eithics committee approval because	**the collection and use of tissue is 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.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**