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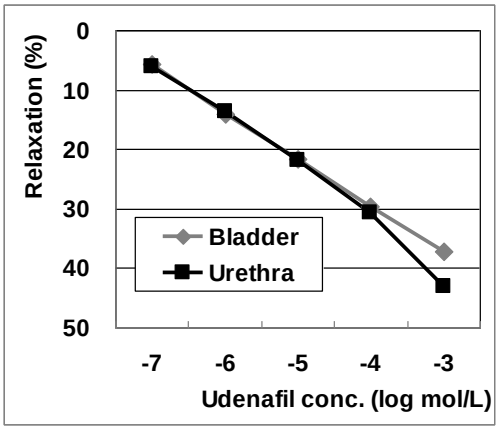
RELAXANT EFFECTS OF UDENAFIL (DA-8159) ON THE BLADDER AND URETHRA: AN IN-VITRO AND IN-VIVO STUDY

Hypothesis / aims of study
Recently, PDE-5 inhibitors have been reported to induce significant relaxation of lower urinary tract tissues. Udenafil (DA-8159) is an oral phosphodiesterase-5 (PDE-5) inhibitor that is developed for the treatment of erectile dysfunction. In vitro and in vivo study was performed to assess the relaxation effect of udenafil on the bladder & urethra and their therapeutic potentials for lower urinary tract symptoms (LUTS)

Study design, materials and methods
For in-vitro study, smooth muscle strips from urinary bladder and proximal urethra were prepared from female New Zealand white rabbits. The strips were mounted under a basal tension of 2 gm in 10 mL organ baths containing a Kreb solution and connected to force transducers. After stabilization, maximal tissue contractions were obtained by the addition of 10^{-4} mol/L phenylepinephrine for urethra strip and 10^{-4} mol/L carbachol for bladder strip . When the contraction was stabilized, a dose-response curve of udenafil was constructed. In vivo study using adult male Sprague-Dawley rats, changes in intravesical pressure and urethral perfusion pressure (UPP) after intra-arterial administration of udenafil (1.0 mg/kg) were monitored using triple lumen catheters.

Results
Figure represented the dose-response curve of the bladder and urethral strips after udenafil (10^{-7} -10^{-3} M). Udenafil significantly relaxed the precontracted bladder and urethra strips in a dose-dependent manner. At 10^{-3} M, udenafil induced a significant relaxation of the bladder strip by 37.1% and urethra strip by 43.2%.



The result of in-vivo study was shown in table. Changes of the UPP after administration of udenafil were not statistically different from the baseline. The inter-contraction interval (ICI) prolonged significantly (from 0.42±0.03 to 0.36±0.02 seconds, p<0.01). The duration of urethral relaxation with high frequency oscillations (Dhfo) prolonged significantly (from 20.20±8.47 to 28.00±9.57 sec, p<0.01.) after udenafil administration. Changes of mean arterial pressure (MAP) were not significant between pre- and post-udenafil administration (p>0.05).

	Before	After	Differences
ICI (sec)	0.42±0.03	0.36±0.02	-14.3%*
UPPbasal (cmH_2O)	32.93±4.43	30.31±4.21	-8.0%
UPPmin (cmH_2O)	4.07±2.99	6.49±2.13	+59.5%
Dhfo (sec.)	20.20±8.47	28.00±9.57	+38.6%*
Pvesdif (cmH_2O)	49.15±19.14	41.92±12.80	-14.7%
MAP (mmHg)	97.8±7.5	95.6±8.5	-2.3%

ICI, intercontraction interval of isovolumic vesical contraction
UPPbasal, baseline urethral perfusion pressure
UPPmin, urethral perfusion pressure during urethral relaxation
Dhfo, duration of high frequency oscillation
Pvesdif, vesical pressure change between peak and baseline pressure
MAP, mean arterial pressure
*, statistically significant

Interpretation of results
Our previous study using same animal model as we did in this experiment reported that tamsulosin, alpha1A blocker, prolonged ICI and Dhfo (1). In this study, udenafil also prolonged ICI and Dhfo, as tamsulosin did. It can be suggested that udenafil may have similar effect to tamsulosin on the lower urinary tract. Udenafil prolonged the Dhfo and decreased frequency of isovolumetric reflex

bladder contraction. It may be anticipated that udenafil improves not only obstructive symptoms but also bladder irritative symptoms, by prolonging the frequency of involuntary bladder contraction.

Concluding message

Udenafil had relaxant effects on the bladder and urethral smooth muscle in both in-vitro and in-vivo study. Clinically, udenafil could be applicated as an effective treatment for LUTS.

References

1. BJU Int (2005) 96:1131-1135

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Care and Use of Laboratory Animals from Korea Food & Drug Administration**