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EFFECTS OF TAMSULOSIN, AN A1-ADRENERGIC ANTAGONIST, AND TAK-802, A NOVEL ACETYLCHOLINESTERASE INHIBITOR, AND THEIR SYNERGISTIC EFFECTS ON THE URODYNAMIC CHARACTERISTICS IN A GUINEA PIG MODEL OF FUNCTIONAL BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

The efficacy of α_1-adrenergic antagonists in the treatment of lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH) is generally attributable to improvement of the urodynamic characteristics and relief of bladder instability. While the latter effect has been partly confirmed in an animal model with partial bladder outlet obstruction (BOO), the former effect has not been well documented in experimental studies using animals, because no suitable animal model has yet been developed to assess the effects of α_1-adrenergic antagonists on the urodynamic characteristics. In this study, we attempted to establish an animal model with functional BOO to model the dynamic component of BPH, and to evaluate the effects of tamsulosin, an α_1-adrenergic antagonist, TAK-802, a novel acetylcholinesterase (AChE) inhibitor with some selectivity for muscarinic actions (1), and of both administered concomitantly on the urodynamic characteristics in this model.

Study design, materials and methods

Male Hartley guinea pigs (300–380 g) were anaesthetized with urethane (1.4 g/kg, i.p.). Two catheters (PE-100) were inserted into the bladder dome, one for recording the intravesical pressure and the other for intravesical infusion of saline (0.3 ml/min). The intravesical pressure and voided volume were measured using a pressure transducer and electronic balance, respectively. Each signal was concomitantly recorded using an MP100A apparatus (Biopac systems). The signal of the voided volume was differentiated to obtain the flow rate. After confirming at least two successive micturition reflexes induced by intravesical infusion of physiological saline, continuous intravenous infusion of phenylephrine, an α_1-adrenergic agonist, was started. The urodynamic parameters were measured prior to and after the drug administration. For evaluation of the effects of tamsulosin and TAK-802, 0.006 mg/animal /min of phenylephrine was administered. The following urodynamic parameters were obtained according to the previous reports (2): maximum flow rate (Qmax), bladder capacity, voided volume, voiding efficiency (=voided volume / bladder capacity×100), maximum intravesical pressure (Pves max) and intravesical pressure at Qmax (Pves(Qmax)).

Results

Effects of phenylephrine: Continuous intravenous infusion of phenylephrine (0.001-0.006 mg/min/animal) decreased the Qmax and voiding efficiency and increased the Pves max and Pves(Qmax) in a dose-dependent manner (Table). The bladder capacity was not affected by phenylephrine.

Table. Effect of continuous infusion of phenylephrine on the Qmax, voiding efficiency and Pves(Qmax) in urethane-anaesthetized guinea pigs.

Phenylephrine	Qmax (ml/sec)		Voiding efficiency (%)		Pves(Qmax) (cmH_2O)	
(mg/animal/min)	Pre	Post	Pre	Post	Pre	Post
Vehicle	0.26 ±0.02	0.22 ±0.02	78.5 ±4.3	74.1 ±4.4	22.7 ±1.6	24.1 ±1.3
0.001	0.23 ±0.04	0.15 ±0.02	64.4 ±9.5	57.3 ±8.9	20.7 ±1.0	25.2 ±2.0
0.003	0.28 ±0.04	0.16 ±0.02**	65.9 ±7.6	63.5 ±7.6	20.0 ±1.2	28.7 ±1.6**
0.006	0.28 ±0.02	0.10 ±0.02**	77.6 ±2.9	33.5 ±5.3**	20.5 ±1.0	35.2 ±1.5**

Pre and post represent values pre and post drug administration, respectively.
Mean ± S.E. ***P*<0.01, v.s. vehicle-treated group (Dunnett's test). N=10.

Effects of tamsulosin and TAK-802: Tamsulosin (0.003 and 0.01 mg/kg, i.v.) and TAK-802 (0.001 and 0.01 mg/kg, i.v.) increased the Qmax and voiding efficiency in a dose-dependent

manner (Figure). The effects were most pronounced in the group that received concomitant administration of both the drugs. When administered alone, tamsulosin decreased, and TAK-802 increased, the Pves max and Pves(Qmax). The effect of TAK-802 of increasing the intravesical pressure was completely abolished by concomitant administration of tamsulosin. Neither of the drugs affected the bladder capacity.

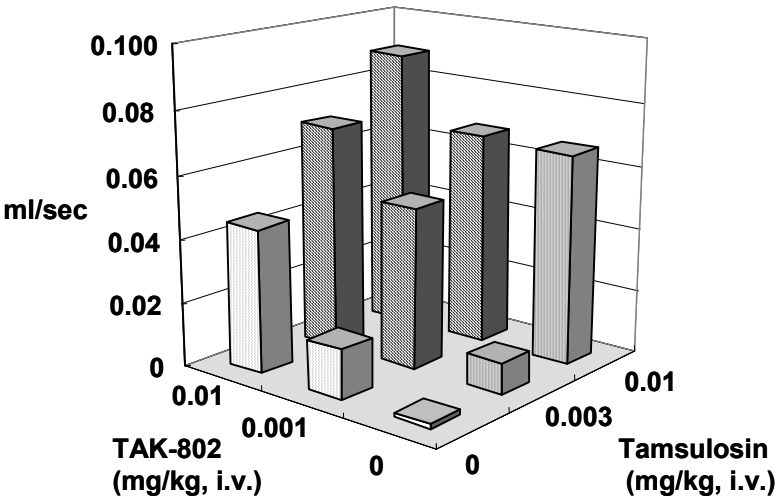

Figure. Effects of tamsulosin and TAK-802, and of both administered concomitantly on the Qmax. Both the drugs significantly affected (two-way ANOVA). Each vertical bar represents the mean of the difference between the values pre and post drug administration value. N=12.

Interpretation of results

The changes in the urodynamic parameters after phenylephrine infusion are attributable to functional urethral constriction, associated with an increase of the urethral resistance. In this animal model, tamsulosin and TAK-802 improved the Qmax and voiding efficiency possibly via different mechanisms, namely relaxation of the smooth muscle tone of the bladder outlet in the case of tamsulosin, and increase of the bladder contractility in the case of TAK-802. Therefore, concomitant administration of both the drugs probably causes synergistic improvement of the urodynamic parameters. Although lowering the urethral resistance by transurethral resection of the prostate or α_1-adrenergic antagonists is the most effective therapy for BPH, pressure flow studies revealed that the LUTS may not necessarily be related to BOO, and may also be affected by detrusor contractility (3). Therefore, concomitant administration of an α_1-adrenergic antagonist and an AChE inhibitor might be of superior efficacy in some patients with BPH, even though cholinergic drugs are not widely employed for the pharmacotherapy of voiding dysfunction. The increase in the Pves max observed following administration of TAK-802 may suggest that AChE inhibitors should be withheld in cases with voiding dysfunction caused by obvious BOO with BPH so as to avoid disorders of the upper urinary tract. However, co-administration of this drug with an α_1-adrenergic antagonist might reduce this risk, because the effect of TAK-802 of increasing the Pves max was completely abolished by concomitant administration of tamsulosin.

Concluding message

Tamsulosin and TAK-802 synergistically improved the urinary voiding function in a model of functional BOO. Concomitant administration of an α_1-adrenergic antagonist and AChE inhibitor might serve as an effective regimen for the pharmacotherapy of LUTS in patients of BPH.

References

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