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SYNERGIC SUPRESSIVE EFFECT OF THE COMBINATION THERAPY WITH SILODOSIN AND IMIDAFENACIN ON NON-VOIDING CONTRACTIONS IN MALE RATS WITH SUB-ACUTE BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Currently, the α_1-adrenoceptor (α_1-AR) antagonist/antimuscarinic combination appears to be a second-line add-on for patients with insufficient symptom relief after monotherapy in males with LUTS associated with bladder outlet obstruction (BOO) (1). However, no urodynamic evaluation has been reported on the effect of the combination therapy. In this study, first, by using precise frequency/volume (FV) and cystometry (CMG) measurements, we evaluated functional changes of LUT in a male rat model with subacute BOO. And then, we investigated that the effect of combination treatment with silodosin, an α1A-AR antagonist, and imidafenacin, a novel anticholinergic agent, on bladder function in this BOO rat model, and compared with that of each monotherapy.

Study design, materials and methods

Sixty male Wistar rats were used, and they were divided into Sham and BOO groups. To make partial BOO, the proximal urethra was ligated with a steel rod (1.2 mm in diameter) using a 3-0 nylon suture and then the steel rod was removed (2). FV measurement was carried out in a metabolic cage without any restraint for 24 hours at 8 days postoperatively (N-8 in each group). A catheter was inserted into the bladder dome under anaesthesia in separate animal. Two days after catheterization, CMG investigations were performed in a conscious and free-moving condition. CMG was repeated 3 times with saline instillation at a rate of 6 mL/hour and the third measurement served as the baseline. Then CMG was repeated after each of cumulative intravenous administrations of silodosin alone (0.1, 1, 10, and 100 μg/kg) or imidafenasin alone (1, 3 and 10 μg/kg) to determine the effective dose of monotherapy. In separate animals, we have investigated the effect of the combination administration of the two drugs, at the dose which had shown no significant effect when administerd alone, on cystometric parameters. The following cystometric parameters were evaluated:

Results

In FV measurement, the BOO showed an increased voiding frequency and decreased mean voided volume and mean flow rate, when compared with the Sham rats. At 10days after operation, the BOO rats had significantly larger bladder weight (0.13 ± 0.03 g, vs 0.3 ± 0.09 g, $p<0.001$). In CMG investigations, increases in the inter-contraction interval, bladder capacity, residual volume, and mean amplitude and number of non-voiding contractions (NVCs) were observed in the BOO rats compared with the Sham rats (Table 1). The number of NVCs in the BOO rats significantly decreased after Silodosin alone at 100 μg/kg and imidafenacin alone at 3 and 10 μg/kg administractions. The combination treatment with a lower-dose of silodosin (10 μg/kg) and imidafenacin (1 μg/kg) showed similar significant effect on the number of NVCs in the BOO rats (Table 2 and Figure 2). Imidafenacin alone at 10 μg/kg significantly increased residual volume and decreased mean flow rate.

Interpretation of results

The present male BOO rat model showed frequent voiding with small voided volumes with low flow rate, large residual volume and increased number and amplitude of NVCs, which reflected detrusor overactivity. These findings mimicked the characteristics of males with LUTS /BOO. Under such condition, silodosin alone as well as imidafenacin alone at the highest dose used inhibited the number of NVCs. When the two drugs were applied as combination at a low dose that was insufficient when used each of them alone, the number of NVCs was significantly decreased, suggesting synergic effect.

Concluding message

The present results indicate a suppressive effect of silodosin and imidafenacin alone on NVCs in male rats with subacute BOO, and a synergic effect of the combination of these two drugs, which is in harmony with clinical beneficial effect of the α_1-AR antagonist/ antimuscarinic combination in males with OAB/BOO.

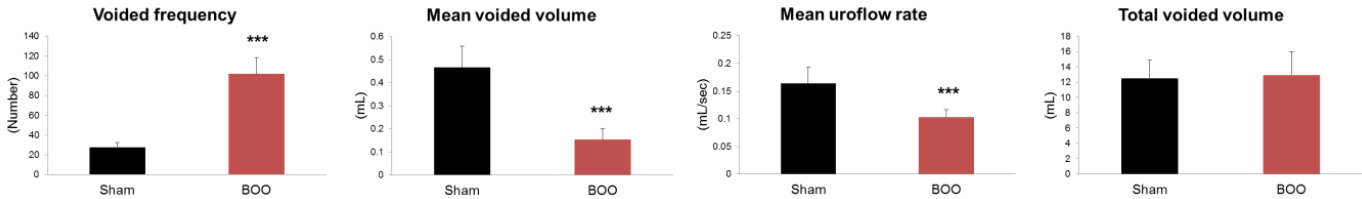

Figure1: Results of the FV measurement in the Sham and BOO rats at 8 days after surgery (n=8 in each). Value are expressed as mean ±SEM. ***p<0.001: significant difference between Sham and BOO rats

Table1: Cystometric parameters in the Sham and BOO rats at 10 days after surgery.

	Intercontraction interval (min)	Voided volume (mL)	Residual Volume (mL)	Bladder Capacity (mL)	Mean uroflow rate (mL/sec)	Number of NVCs	Amplitudes of NVCs(cmH2O)
Sham (n= 8)	8.46±3.72	0.95±0.39	0.10±0.08	1.05±0.43	0.16±0.01	1.11±1.17	2.48±2.54
BOO (n= 8)	19.00±5.02***	0.77±0.55	1.624±0.79**	2.4±0.42***	0.05±0.05***	6.38±1.30***	6.25±1.26**

Value are expressed as mean ±SEM. ***p<0.001: significant difference between the Sham and BOO rats.

Table2: The effect of silodosin alone, imidafenacin alone, and their combination on cystometric parameter in the Sham and BOO rats.

Treatment	Dose (μg/kg)	Intercontraction interval (min)	Voided volume (mL)	Residual Volume (mL)	Bladder Capacity (mL)	Mean uroflow rate (mL/sec)	Number of NVCs	Amplitudes of NVCs(cmH2O)
Sham silodosin: (n= 7)	before	5.44±2.77	0.63±0.23	0.05±0.05	0.67±0.24	0.14±0.03	0.5±0.76	1.46±2.04
	0.1	5.71±3.00	0.68±0.34	0.04±0.03	0.71±0.33	0.11±0.05	0	0
	1	4.91±2.02	0.65±0.26	0.03±0.02	0.68±0.25	0.14±0.03	0.5±1.07	1.11±2.16
	10	5.52±3.30	0.71±0.29	0.04±0.06	0.75±0.29	0.13±0.03	0.36±0.74	1.02±1.89
	100	6.33±2.94	0.75±0.27	0.03±0.03	0.78±0.26	0.12±0.04	1.0±1.31	2.44±2.71
BOO silodosin: (n= 7)	before	18.57±5.26	0.81±0.28	1.57±0.84	2.38±0.45	0.06±0.05	6.0±0.81	5.88±0.78
	0.1	17.90±7.53	0.81±0.71	1.33±0.84	2.14±0.94	0.06±0.05	5.86±1.35	5.91±1.50
	1	16.46±2.03	0.87±0.69	1.21±0.61	2.08±0.81	0.06±0.05	5.14±2.54	6.16±1.59
	10	16.70±3.30	0.94±0.73	1.10±0.40	2.04±0.86	0.07±0.05	5.43±1.51	5.56±0.80
	100	17.80±2.94	1.10±0.70	1.14±0.41	2.24±0.79	0.07±0.05	2.71±1.89##	5.01±2.47
Sham imidafenacin: (n= 8)	before	7.74±4.12	0.93±0.42	0.10±0.09	1.17±0.59	0.16±0.06	1.63±0.92	3.88±0.51
	1	6.45±3.23	0.86±0.36	0.09±0.07	1.00±0.49	0.14±0.05	2.00±1.60	2.63±2.55
	3	7.96±3.69	0.95±0.34	0.15±0.20	1.15±0.6	0.14±0.04	1.38±1.41	2.67±2.47
	10	8.48±5.20	0.81±0.42	0.32±0.20##	1.18±0.68	0.12±0.04#	1.00±1.41	1.54±2.17
BOO imidafenacin: (n= 8)	before	21.02±8.17	1.02±0.49	1.49±1.15	2.52±1.02	0.06±0.02	5.50±1.31	5.90±2.50
	1	16.79±4.09	0.77±0.54	1.21±0.88	1.99±0.47	0.06±0.04	4.13±1.55	6.10±1.83
	3	20.47±8.39	0.68±0.47	1.85±165	2.53±1.30	0.05±0.03	3.25±2.12##	5.76±3.64
	10	23.68±11.79	0.54±0.46#	2.19±1.64	2.73±1.4	0.05±0.04	3.63±1.60#	6.08±2.18
Sham combination Silodosin & Imidafenacin: (n= 8)	before	7.23±1.77	0.93±0.10	0.15±0.13	1.08±0.20	0.14±0.01	0.17±0.41	0.83±2.02
	10 1.0	8.28±1.96	0.80±0.23	0.16±0.14	0.96±0.30	0.13±0.04	0	0
BOO combination Silodosin & imidafenacin: (n = 8)	before	21.00±14.22	0.57±0.38	2.09±1.33	2.67±1.42	0.04±0.03	6.00±2.00	5.02±0.81
	10 1.0	14.71±7.09	0.29±0.13	1.40±0.96	1.69±0.86	0.03±0.02	3.14±2.67##	3.38±2.53

Value are expressed as mean ±SEM. #p<0.05, ##p<0.01: significant differences between before and after drug-administrations.

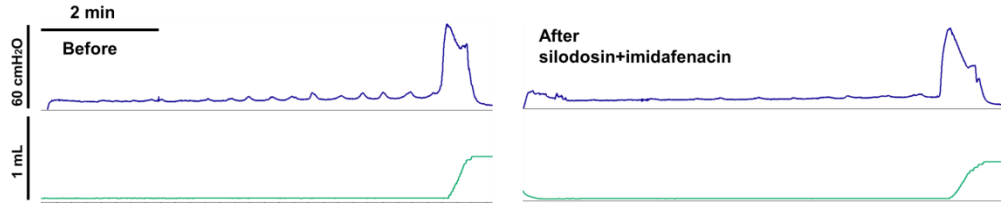

Figure 2: Representative cystometric recordings in a conscious restraint male rat with BOO before (left tracing) and after (right tracing) intravenous combined-administration of silodosin (10 μg/kg) and imidafenacin (1 μg/kg).

References

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Disclosures

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