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EFFICACY OF COMBINATION THERAPY OF B3-ADRENOCEPTOR STIMULATION AND BLOCKADE OF MUSCARINIC ACETYLCHOLINE RECEPTORS IN RATS WITH OXOTREMORINE METHIODIDE-INDUCED BLADDER OVERACTIVITY

Hypothesis / aims of study
A combination of β_3-adrenoceptor (AR) stimulation and blockade of muscarinic acetylcholine (M) receptors seems to be an effective way to relax the bladder because M_2-receptor blockade and β_3-AR stimulation contribute to bladder relaxation by enhancing adenylate cyclase activity and M_3-receptor blockade inhibits bladder contraction during the filling phase. Thus we investigated the efficacy of a combination of selective β_3-AR agonist (mirabegron) and M-receptor antagonists (M_2-selective antagonist; methoctramine hemihydrate and M_3-seletive antagonist; 4-DAMP) compared with either agent given alone using rats with oxotremorine methiodide (oxo-M: non-selective M-agonist)-induced bladder overactivity.

Study design, materials and methods
Cystometry was performed in conscious female Sprague-Dawley rats with intravesical instillation of oxo-M (200μM). Either mirabegron (0.3-3mg/kg), methoctramine (0.1-1mg/kg) or 4-DAMP (0.03-0.3mg/kg) was cumulatively applied intravenously to each animal, respectively. Then, the effects of combined application of mirabegron (3mg/kg) plus methoctramine (1mg/kg) or mirabegron (3mg/kg) plus 4-DAMP (0.3mg/kg) on cystometric parameters were compared with those of single agent application.

Results
Intravesical instillation of oxo-M induced bladder overactivity evidenced by decreased threshold pressure and bladder capacity. In oxo-M-treated rats, the single application of mirabegron (1, 3mg/kg), methoctramine (0.3, 1mg/kg) or 4-DAMP (0.1, 0.3mg/kg) decreased baseline pressure and increased bladder capacity. In addition, decreased threshold pressure and maximal voiding pressure were also seen after the administration of 4-DAMP (0.3mg/kg) (Table 1). The combined treatment of mirabegron and 4-DAMP induced a larger increase in bladder capacity compared to monotherapy of either drug although there was no significant difference in changes of cystometric parameters between combination therapy and monotherapy of mirabegron and methoctramine (Table 2).

Interpretation of results
The recent phase II study (Symphony) that examined concerning the efficacy of combined treatment of mirabegron and solifenacin (M_3-seletive antagonist) have shown that mirabegron combination therapy with solifenacin demonstrated greater efficacy than solifenacin alone on mean voided volume and micturition frequency in patients with overactive bladder [1], which is consistent with the results of this study. In addition, the present study indicated that the combination therapy of mirabegron and methoctramine (M_2-selective antagonist) has no additional effects on bladder relaxation because mirabegron and methoctramine similarly modulate adenylate cyclase activity to induce bladder relaxation, as shown by decreased baseline pressure. On the other hand, the additive effects of 4-DAMP (M_3-seletive antagonist) to mirabegron could be explained by its inhibitory action on efferent function during the voiding phase as shown by decreased maximal voiding pressure and also on afferent function as evidenced by decreased baseline and threshold pressures [2].

Concluding message
These results suggest that the combination therapy of selective β_3-AR agonists and M_3-seletive antagonists is more effective compared to monotherapy for the treatment of overactive bladder. On the other hand, the efficacy of selective β_3-AR agonists may not be increased by the addition of M_2-seletive antagonists.

Table 1. Changes in cystometric parameters during cumulative application of each agent

		Mean (SD) BP, cmH_2O	Mean (SD) TP, cmH_2O	Mean (SD) MVP, cmH_2O	Mean (SD) BC, sec	Mean (SD) PVR, ml
Mirabegron (β_3 agonist)	Vehicle	5.8 (1.6)	8.8 (3.1)	21.8 (5.9)	0.142 (0.019)	0.022 (0.004)
	0.3 mg/kg	5.4 (1.2)	8.3 (3.0)	22.5 (7.3)	0.148 (0.022)	0.022 (0.004)
	1 mg/kg	4.8 (1.2)**	8.0 (0.3)	22.6 (9.1)	0.176 (0.030)**	0.022 (0.004)
	3 mg/kg	4.5 (1.3)**	7.7 (2.2)	19.7 (6.4)	0.200 (0.029)**	0.022 (0.004)
Methoctramine (M_2 antagonist)	Vehicle	5.9 (0.6)	7.5 (0.5)	22.3 (4.3)	0.116 (0.030)	0.022 (0.004)
	0.1 mg/kg	6.0 (0.6)	7.7 (0.4)	22.8 (3.9)	0.114 (0.032)	0.022 (0.004)
	0.3 mg/kg	5.1 (0.6)**	8.0 (0.4)	19.3 (2.4)	0.154 (0.027)**	0.024 (0.009)
	1 mg/kg	4.6 (0.8)**	7.8 (0.2)	18.7 (1.7)	0.160 (0.034)**	0.024 (0.008)
4-DAMP (M_3 antagonist)	Vehicle	5.2 (1.4)	8.9 (3.1)	21.7 (5.3)	0.150 (0.062)	0.022 (0.004)
	0.03 mg/kg	4.7 (1.0)	8.6 (2.5)	21.0 (3.2)	0.156 (0.065)	0.022 (0.004)
	0.1 mg/kg	4.1 (1.1)**	7.9 (1.3)	19.2 (3.7)	0.204 (0.076)**	0.022 (0.004)
	0.3 mg/kg	3.7 (1.0)**	7.2 (1.6)*	17.4 (3.6)**	0.224 (0.099)**	0.024 (0.009)

BP: baseline pressure, TP; threshold pressure, MVP; maximal voiding pressure, BC; bladder capacity, PVR; post-voided residual urine volume
*; P<0.05, **; P<0.01 compared with vehicle

Table 2. Comparison of the efficacy of combination therapy versus monotherapy

	Mean (SD) BP, cmH_2O	Mean (SD) TP, cmH_2O	Mean (SD) MVP, cmH_2O	Mean (SD) BC, sec	Mean (SD) PVR, ml
Mirabegron	5.5 (0.8)	9.9 (1.7)	21.9 (3.7)	0.168 (0.048)	0.026 (0.005)
Mirabegron + Methoctramine	5.2 (0.8)	8.9 (1.2)	19.9 (2.8)	0.172 (0.049)	0.024 (0.004)
Methoctramine	6.0 (2.9)	10.0 (3.9)	26.1 (6.5)	0.182 (0.039)	0.022 (0.004)
Methoctramine + Mirabegron	5.5 (2.7)	9.3 (3.6)	24.7 (5.5)	0.186 (0.038)	0.022 (0.004)
Mirabegron	3.9 (1.3)	8.0 (1.3)	18.0 (1.1)	0.146 (0.061)	0.024 (0.005)
Mirabegron + 4-DAMP	3.9 (1.4)	7.6 (1.1)	14.6 (2.2)**	0.194 (0.097)*	0.022 (0.004)
4-DAMP	3.3 (0.9)	6.5 (1.2)	18.0 (4.1)	0.216 (0.045)	0.030 (0.001)
4-DAMP + Mirabegron	3.2 (0.8)	6.6 (1.2)	17.6 (4.1)	0.278 (0.043)*	0.026 (0.005)

BP: baseline pressure, TP; threshold pressure, MVP; maximal voiding pressure, BC; bladder capacity, PVR; post-voided residual urine volume
*; P<0.05, **; P<0.01 compared with each monotherapy

References

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