

## EFFECTS OF COMBINATION TREATMENT WITH FESOTERODINE AND MIRABEGRON ON URINARY BLADDER FUNCTIONS OF PELVIC CONGESTION MODEL IN RATS

### Hypothesis / aims of study

Muscarinic receptor antagonists and  $\beta_3$  adrenoceptor agonist are the currently recommended medicines for pharmacologic treatments of overactive bladder. The effect of combination treatment with antimuscarinics and mirabegron had been studied in animal models. However the effect of combination treatment of fesoterodine and mirabegron has not been investigated yet. The present study examined whether the combination does exert additive effect on the **storage** symptom in female rats with pelvic congestion. Pelvic congestion (PC) was developed through ligation of the bilateral common iliac veins and uterine veins, which led to induced frequent urination and decreased locomotor activity (a marker of pain)<sup>1)</sup>. In this study, 5-hydroxymethyl tolterodine (5-HMT) which is the main active metabolite of fesoterodine, was used to determine the effect of combination with mirabegron, since fesoterodine itself is inactive and rapidly converted after absorption. In addition, expressions of muscarinic receptor subtypes ( $M_2$  and  $M_3$ ) were examined.

### Study design, materials and methods

Female Sprague-Dawley rats (body weight: 250-300 g) were used, and PC was developed in accordance to a published method<sup>1)</sup>. Expressions of  $M_2$ , and  $M_3$  receptor subtypes were detected by real time RT-PCR assay in the urothelium and detrusor. The parameters investigated by single cystometry were: bladder capacity (BC), micturition pressure (MP), and threshold pressure (TP). 5-HMT (0.01 mg/kg) and mirabegron (0.1 mg/kg) were intravenously administrated independently or in combination. Differences within group was assessed by U-test and between groups were assessed by ANOVA;  $p < 0.05$  was significant.

### Results

Compared to the sham operated rats, the expression of both  $M_2$  and  $M_3$  receptor subtypes in the urothelium were higher in PC rats (2.17 times in  $M_2$  and 1.87 times in  $M_3$  vs. sham). BC was significantly smaller in PC rats ( $0.55 \pm 0.05$ ) than in sham rats ( $0.73 \pm 0.14$  mL,  $P < 0.01$ , U-test) and no statistical differences were observed in the MP and TP between PC and sham rats. In PC rats, BC was significantly increased from baseline in combination treatment group but not in 5-HMT or mirabegron monotherapy groups ( $P < 0.01$ , Table 1). Compared to the monotherapy group of 5-HMT or mirabegron, a statistically significant increase in BC was observed in the combination treatment group ( $P < 0.05$ , Table 1, Figure 1). MP and TP were not significantly changed between treatment groups (Table 1).

### Interpretation of results

In the PC model, high mRNA expression of both  $M_2$  and  $M_3$  receptor subtypes in the urothelium were observed and the baseline BC was smaller compared to the sham. PC model rat could be categorized a non-neurogenic storage dysfunction model. The combination treatment with 5-HMT and mirabegron increased BC compared to both monotherapy groups. The potential synergic effects in the current data suggests that the combination of fesoterodine with mirabegron is a positive therapeutic alternative for OAB patients who did not respond or show only suboptimal responses to monotherapy with antimuscarinics or mirabegron.

### Concluding message

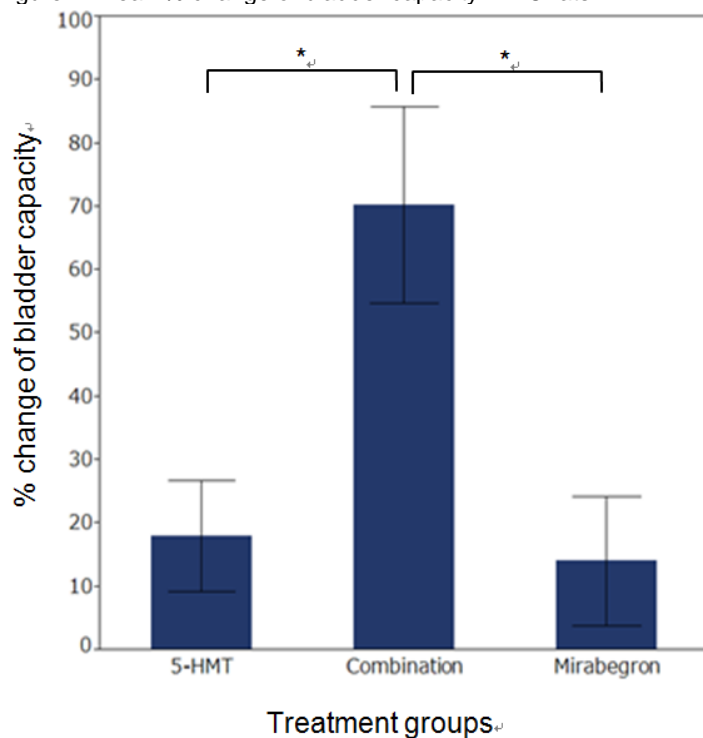
Combination treatment with 5-HMT (blocking  $M_2$  /  $M_3$  receptors) and mirabegron (enhancing relaxation effects by  $\beta_3$  adrenoceptor stimulation) have improved the bladder function (storage symptom) in PC model rats.

Table 1. Mean change of cystometric parameters in PC rats

Variables	5-HMT (n=8) Mean $\pm$ SE	Mirabegron (n=8) Mean $\pm$ SE	Combination (n= 8) Mean $\pm$ SE	P value combination vs. (Dunnett's test)
BC (mL)	$0.07 \pm 0.03$	$0.07 \pm 0.05$	$0.37 \pm 0.07^*$	$P < 0.01$ : 5-HMT $P < 0.01$ : mirabegron
MP (cmH <sub>2</sub> O)	$-3.85 \pm 1.08$	$-1.65 \pm 1.77$	$-7.02 \pm 2.20$	$P > 0.05$ : 5-HMT $P > 0.05$ : mirabegron
TP (cmH <sub>2</sub> O)	$-0.17 \pm 0.37$	$0.20 \pm 0.13$	$-0.01 \pm 0.32$	$P > 0.05$ : 5-HMT $P > 0.05$ : mirabegron

\*:  $P < 0.01$ , change from baseline (ANOVA)

Figure 1. Mean % change of bladder capacity in PC rats



\*:  $P < 0.05$ , between combination treatment and each monotherapy group (Dunn's test). Data are given as mean  $\pm$  SE

#### References

1. Nishijima S., et al. Characteristics of the pelvic congestion, model rat with urinary frequency. *Nihon Hinyokika Gakkai Zasshi*. 2013; 104: 423 (Abstract in Japanese)

#### Disclosures

**Funding:** Pfizer Japan Inc. **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The Institutional Animal Care and Use Committee at University of Shizuoka, and the Institutional Animal Care and Use Committee at the President of University of the Ryukyu