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ADDITIVE EFFECTS FOR INCREASED BLADDER STORAGE FUNCTION WITH THE ANTIMUSCARINIC DRUG SOLIFENACIN AND THE SELECTIVE B3-ADRENERGIC AGONIST MIRABEGRON IN TWO RAT MODELS FOR IN VIVO BLADDER FUNCTION.

Hypothesis / aims of study

With the recent introduction of the selective β_3-adrenergic agonist mirabegron as first representative of a new drug class for treatment of overactive bladder (OAB), the possibility of enhancing efficacy in the treatment of OAB by combination treatment with the current standard, antimuscarinics, can be considered. Antimuscarinics and β_3-adrenergic agonists act through distinct molecular pathways to increase bladder storage function, while it can be expected that there will be no interaction during the voiding phase. Thus additive effect/synergism on storage parameters on concomitant use may be hypothesized. This hypothesis was tested on storage parameters in two bladder function models in rats.

Study design, materials and methods

For study 1, female Wistar rats were used. Under pentobarbital (50 mg/kg, ip) anesthesia, the ureters on both side were cut and a polyethylene catheter was inserted into the bladder via the urethra and connected to a pressure transducer and a syringe filled with saline via a three way connector. For iv administration of drugs a catheter was inserted in a femoral vein. Baseline intravesical pressure (IVP) was adjusted at ± 6 cm H_2O (just below threshold of micturition) by infusing saline into the bladder via the catheter. After stabilization of baseline IVP, mirabegron (0.01 mg/mL/kg) and/or solifenacin (0.1, 0.3 mg/mL/kg), or vehicle, were given. IVP was assessed just before and 2 min after drug/vehicle dosing and the difference was calculated as means/treatment group and evaluated for statistical differences versus solifenacin alone dose groups by Dunnett's multiple comparison test at $P<0.05$ for statistical significance.

For study 2, male Sprague-Dawley rats were used. Cerebral infarction was introduced by middle cerebral artery occlusion [1]. Rats were anesthetized with 3% isoflurane during surgery. Sham rats underwent a midline neck incision without the intraluminal occlusion procedure. One day after surgery, animals were orally loaded with water (30 mL/kg). Voided weight was continuously recorded for animals in individual cages equipped with an automated balance urine collector system and electronic registration. Animals were excluded when mean voided weight was □ 1.00 g, or micturition frequency for 1.5 h after water loading was ≤ 2, or total voided urine weight for 1.5 h after water loading was ≤ 20% of loaded volume. The following groups were studied: Sham+ vehicle; control+ vehicle; mirabegron 0.3, 1, 3 mg/3 mL/kg po; solifenacin 0.03, 0.1, 0.3 mg/mL/kg iv; combination treatment of mirabegron 1 mg/3 mL/kg po+ solifenacin 0.1 mg/mL/kg iv. Mean voided volume (MVV) was assessed for 1.5 h after water loading in all animals and evaluated for statistical differences for each treatment group using Student's t-test for single comparisons and Dunnett's test for multiple comparisons, using $P<0.05$ as the criterion for statistical significance.

Results

Study 1: In anesthetized rats, single doses of mirabegron (0.01 mg/kg iv) or solifenacin (0.3 mg/kg iv) decreased resting IVP. Concomitant use of mirabegron (0.01 mg/kg iv) and solifenacin (0.3 mg/kg iv) additively decreased resting IVP compared with single use of either drug:

Figure 1A:

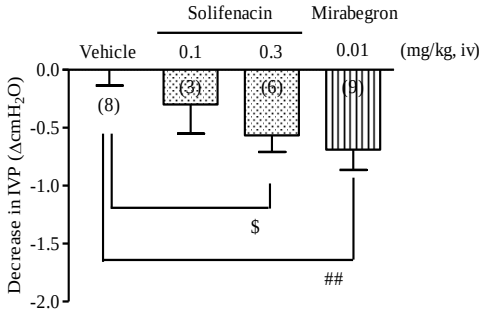
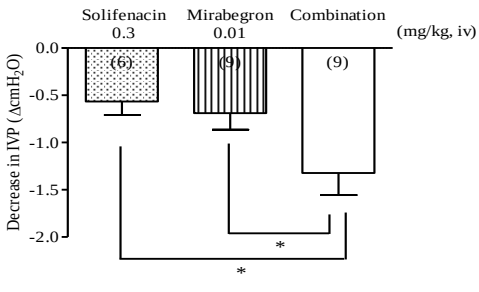


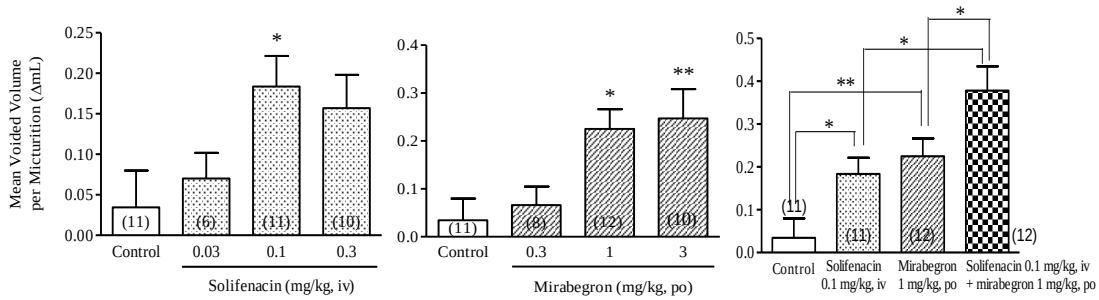
Figure 1B:



(Legend: $: $P<0.05$ with Dunnett's multiple comparison test; */##: $P<0.05/0.01$ with Student's t-test; (x) denotes number of animals tested; data are given as means ± SEM)

Study 2: In water-loaded rats with cerebral infarction, MVV was significantly lower ($P<0.01$: Student's t-test) than in Sham animals. Single dose administration of solifenacin significantly increased MVV at 0.1 mg/kg iv. (Fig 2A) and single dose administration of mirabegron significantly increased MVV at 1 mg/kg po or more (Fig. 2B). Concomitant use of mirabegron (1 mg/kg po) and solifenacin (0.1 mg/kg iv) additively increased MVV significantly compared with either single doses of mirabegron or solifenacin (Fig. 2C)

Figure 2A: Figure 2B: Figure 2C:



(Legend for Figure 2A&2B: */**: P<0.05/0.01 with Dunnett's multiple comparison test; (x) denotes number of animals tested; data are given as means ± SEM)
(Legend for Figure 2B: */**: P<0.05/0.01 with Student's t-test;; (x) denotes number of animals tested; data are given as means ± SEM)

Interpretation of results

Mirabegron and solifenacin were found to decrease bladder pressure in rats under low pressure isovolumetric conditions, which shows the capability for both drugs to promote bladder storage in the early phase of the voiding cycle. Combination of both drugs showed additive effects at this condition. In addition, while both drugs individually showed efficacy in the neurogenic bladder hyperactivity model, concomitant dosing further increased functional bladder capacity of the animals. The combi effect expressed higher efficacy than observed for other drugs in this model [2]. While this model is reasonably predictive to test drug efficacy in bladder hyperactivity syndromes [3], the combined data set provides proof of mechanism for additive effect of the combination to promote bladder storage, with potential relevance for OAB patients.

Concluding message

The results from these non-clinical studies suggest that combination treatment of mirabegron and solifenacin could offer potential for patients in need for higher efficacy treatment of their OAB symptoms, to be confirmed in a clinical setting.

References

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2. Nakada N, et al. J Pharmacol Exp Ther 2000; 293:921-8
3. Soler R, et al. Meth Pharmacol Toxicol 2012;411-31

Disclosures

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