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EFFECTS OF A NOVEL EP2 AND 3 RECEPTOR DUAL AGONIST (ONO-8055) ON LOWER URINARY TRACT FUNCTION IN NORMAL RATS

Hypothesis / aims of study

A novel EP2 and 3 receptor dual agonist (ONO-8055) contracts bladder smooth muscle and relaxes urethral smooth muscle in muscle strip studies, while this agonist decreases the residual urine rate (RUR) in awake cystometry in lumbar canal stenosis (LCS) rats, probably via a decrease in maximum cystometric capacity (MCC) as well as in intraurethral perfusion pressure (Pura) (1). On the other hand, its effects on the lower urinary tract function in normal rats remains to be investigated. In the present study, our hypothesis was that ONO-8055 would augment bladder contractility, decrease bladder capacity, and lower Pura in the awake condition.

Study design, materials and methods

Female normal Wister rats were used.

Experiment 1: Two days after insertion of a cystostomy catheter, cystometries (CMGs) were performed in an awake restrained condition. Vehicle or ONO-8055 was orally administered, and CMGs were done 1, 2, and 4 hours after administration. The following cystometric parameters were investigated: baseline intravesical pressure (Pbase), threshold intravesical pressure (Pth), maximal intravesical pressure during voiding (Pmax), MCC, vesical complaiance (MCC ÷ (Pth - Pbase)), postvoid residual urine volume (PVR), and RUR (PVR ÷ (voided volume +PVR) x 100).

Experiment 2: After transvesical insertion of a catheter for Pura measurement, Pura was measured until 2 hours after oral administration of the vehicle or ONO-8055. The baseline Pura was obtained as post-mortem stable Pura, and measured Pura was adjusted by the baseline Pura (2).

Measured data between pre- and post-administration were compared (paired t-test) as well as between vehicle group and ONO-8055 groups (ANOVA followed by Dunnet's test). $p < 0.05$ was considered as statistically significant.

Table. Changes in cystometric parameters before and after vehicle or ONO-8055 administration

	Pbase mmHg	Pth mHg	MCC mL	Vcomp mL/cmH2O	Pmax mmHg	VV mL	PVR mL	RUR %
Vehicle								
1h	-0.17 ± 0.29	0.45 ± 0.50	0.01 ± 0.13	-0.10 ± 0.10	-0.90 ± 1.22	-0.02 ± 0.16	-0.03 ± 0.04	-1.47 ± 4.59
2h	-0.20 ± 0.21	-0.08 ± 0.47	0.04 ± 0.12	-0.04 ± 0.08	-1.80 ± 1.05	0.03 ± 0.13	-0.03 ± 0.03	-1.59 ± 1.94
4h	-0.37 ± 0.28	0.05 ± 0.83	0.03 ± 0.12	-0.06 ± 0.10	-2.03 ± 1.41	-0.05 ± 0.14	-0.03 ± 0.03	-0.48 ± 2.45
8055 0.01 mg/kg								
1h	0.30 ± 0.29	-0.45 ± 0.50	0.01 ± 0.13	0.11 ± 0.10	1.03 ± 1.22	0.01 ± 0.16	0.01 ± 0.04	0.70 ± 4.59
2h	0.26 ± 0.21	-0.15 ± 0.51	-0.07 ± 0.12	0.05 ± 0.08	0.40 ± 1.05	-0.06 ± 0.13	0.00 ± 0.03	0.43 ± 1.94
4h	-0.02 ± 0.28	-0.33 ± 0.68	-0.18 ± 0.12	0.03 ± 0.10	-0.68 ± 1.41	-0.18 ± 0.14	0.00 ± 0.03	0.79 ± 2.45
8055 0.03 mg/kg								
1h	-0.05 ± 0.24*	1.16 ± 0.42	-0.03 ± 0.11	-0.12 ± 0.09*	2.34 ± 1.03*	0.01 ± 0.14	-0.05 ± 0.04	-2.06 ± 3.88
2h	-0.34 ± 0.18	-0.29 ± 0.55	-0.11 ± 0.10	-0.08 ± 0.06	1.52 ± 0.89	-0.03 ± 0.11	-0.08 ± 0.02	-4.76 ± 1.64*
4h	0.05 ± 0.23	-0.67 ± 0.51	-0.13 ± 0.10	0.00 ± 0.09	1.70 ± 1.12	-0.10 ± 0.12	-0.03 ± 0.03	-2.05 ± 2.07
8055 0.1 mg/kg								
1h	0.71 ± 0.26	0.94 ± 0.46	-0.11 ± 0.12	-0.01 ± 0.09	2.63 ± 1.11	-0.11 ± 0.15	0.00 ± 0.04	0.21 ± 4.19
2h	0.17 ± 0.19	-0.42 ± 0.57	-0.33 ± 0.11	-0.05 ± 0.07	1.88 ± 0.96	-0.35 ± 0.12	0.02 ± 0.03	2.28 ± 1.77
4h	0.10 ± 0.25	-0.58 ± 0.63	-0.34 ± 0.11	0.09 ± 0.09	0.10 ± 1.28	-0.33 ± 0.13	0.00 ± 0.03	0.28 ± 2.23
8055 0.3 mg/kg								
1h	0.33 ± 0.26	-0.21 ± 0.46	-0.31 ± 0.12	0.09 ± 0.09	-1.52 ± 1.11	-0.43 ± 0.15	0.00 ± 0.04	3.52 ± 4.19
2h	0.27 ± 0.19	-0.54 ± 0.44	-0.43 ± 0.11*,**	0.06 ± 0.07	-1.85 ± 0.96*	-0.38 ± 0.12*	-0.05 ± 0.03	-1.96 ± 1.77
4h	0.19 ± 0.25	-0.50 ± 0.43	-0.49 ± 0.12*,**	-0.01 ± 0.09	-0.31 ± 1.28	-0.43 ± 0.13*	-0.06 ± 0.03	-2.71 ± 2.23

Data are shown as mean ± S.E.M., *p <0.05 (vs. pre-), **p <0.05 (vs. vehicle), 8055; EP2 and 3 dual agonist

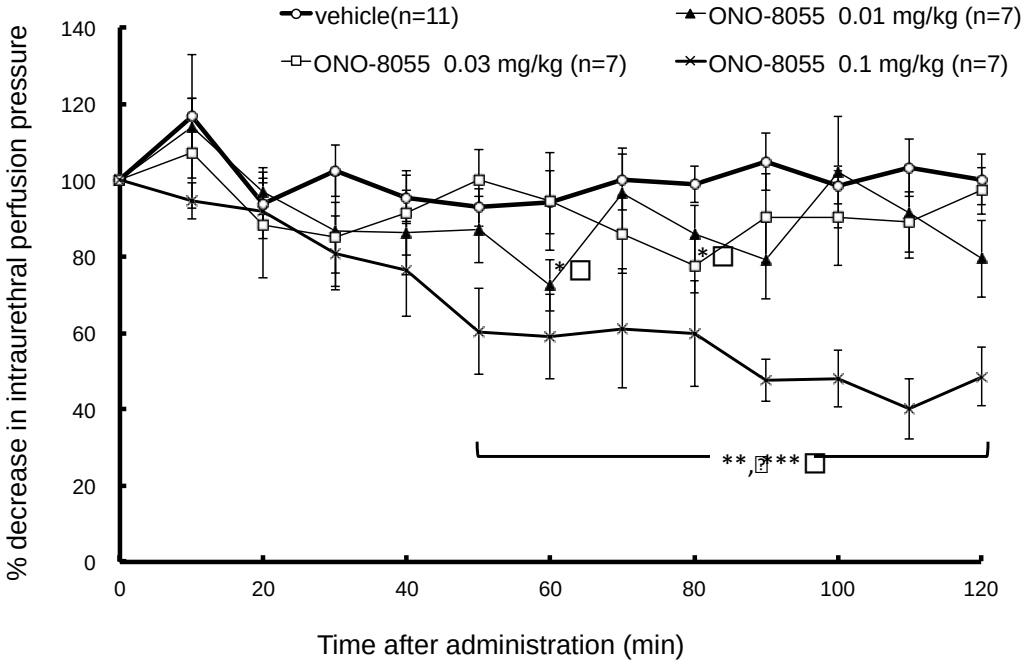

Figure. Effects of vehicle or ONO-8055 on intraurethral perfusion pressure
*p <0.05 (vs. pre-), **p <0.05 (vs. pre-, 0.1mg/kg), ***p <0.05 (vs. vehicle, 0.1mg/kg), bar indicates S.E.M.

Results

Experiment 1 (Table): There were no significant changes in CMG parameters in the vehicle group. Although Pmax was slightly increased (0.5 to 2.5 mmHg) at the dose of 0.01, 0.03, and 0.1 mg/kg but slightly decreased (2 mmHg) at the dose of 0.3mg/kg, there were no significant differences in mean changes between vehicle group and ONO-8055 groups. MCC was slightly decreased in ONO-8055 groups except 1 hour after administration of 0.01 mg/kg ONO-8055 administration, but a significant difference in mean changes was demonstrated only between the vehicle group and the group administered 0.3 mg/kg ONO-8055.
Experiment 2 (Figure): Pura was decreased by 92.8% in the vehicle group. On the other hand, in the ONO-8055 groups Pura was decreased by 72.5, 77.6, and 40.1% after doses of 0.01, 0.03, and 0.1 mg/kg, respectively. There were significant differences only between the groups administred the vehicle and 0.1 mg/kg of ONO-8055.

Interpretation of results

ONO-8055 did not augment bladder contractility in normal rats or LCS rats. Although MCC and Pura were decreased, these effects were demonstrated at doses that were thirty and ten times higher than the doses in LCS rats for MCC and Pura, respectively (1). It is suggested that a pathway via EP2 and 3 receptors does not play an important role in lower urinary tract function in normal rats and that this pathway would be more susceptible in LCS rats. In addition, it was conceivable that ONO-8055 affects the bladder afferent system rather than the detrusor itself.

Concluding message

EP2 and 3 receptor dual agonist did not augment bladder contractility. Decreases in MCC and Pura were revealed only after administration of the highest dose of ONO-8055.

References

1. J Urol doi: 10.1016/j.juro.2016.02.064.
2. PLOS One 9: e93230, 2014.

Disclosures

Funding: Ono Pharmaceutical Co. Ltd., Japan **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Animal Experimental Committee of Ono Pharmaceutical Co., Ltd.