

## URODYNAMIC EFFECTS OF A NOVEL EP<sub>1</sub> RECEPTOR ANTAGONIST IN NORMAL RATS AND RATS WITH BLADDER OUTLET OBSTRUCTION

### Hypothesis / aims of study

Prostanoids, and in particular PGE<sub>2</sub>, have been implicated as endogenous modulators of bladder function, both in the normal physiological state and under pathophysiological conditions. Prostanoid synthesis occurs locally in both bladder muscle and mucosa, and is initiated by various physiological stimuli, such as stretch of the detrusor muscle and nerve stimulation, and also by injuries and mediators of inflammation. Previous studies in mice have suggested that prostaglandin E<sub>2</sub> and its EP<sub>1</sub> receptor may be involved in the pathophysiology of different bladder disorders. The purpose of this study was to investigate if a new EP<sub>1</sub> receptor antagonist, PF-2907617-02, can influence the regulation of normal micturition in rats, and if it affects bladder function in animals with bladder outlet obstruction (BOO).

### Study design, materials and methods

The study was performed in normal female Sprague Dawley rats, and rats with a moderate, experimentally induced BOO of 2 weeks duration. All animals underwent continuous cystometry in the awake state. PF-2907617-02 was given intravenously at doses of 0.1 and 1.0 mg.kg<sup>-1</sup> to normal rats, and at a dose of 1.0 mg.kg<sup>-1</sup> to BOO animals. In a group of normal rats, detrusor overactivity was produced by intravesical instillation of PGE<sub>2</sub>.

### Results

In normal rats, PF-2907617-02 (1 mg.kg<sup>-1</sup>) significantly increased bladder capacity, micturition volume, and micturition interval, but had no effect on other urodynamic parameters (Table 1). The lower dose of PF-2907617 (0.1 mg.kg<sup>-1</sup>) was without effect. Intravesical PGE<sub>2</sub> (50 uM) induced detrusor overactivity. The antagonist significantly reduced the stimulatory effects of PGE<sub>2</sub> at 0.1 and 1.0 mg.kg<sup>-1</sup> (Table 1). In obstructed animals, PF-2907617-02 significantly increased micturition interval, but not bladder capacity and residual volume. The drug also decreased the frequency and amplitude of non-voiding contractions (Table 2).

### Interpretation of results

PF-2907617-02 significantly increased bladder capacity, voided volumes and micturition intervals in normal animals. This suggests that PGE<sub>2</sub> is produced during bladder filling and via the EP<sub>1</sub> receptor is involved in the control of the initiation of the micturition reflex. This may be the case also in BOO animals. A previous urodynamic study on EP<sub>1</sub> knockout mice suggested that the EP<sub>1</sub> receptor played a role also in the development of detrusor overactivity caused by PGE<sub>2</sub> and outlet obstruction. The results obtained with PF-2907617-02 seem to confirm this assumption.

### Concluding message

The EP<sub>1</sub> receptor may be involved in the initiation of the micturition reflex, both in normal rats and in animals with BOO. It may also contribute to the generation of detrusor overactivity after BOO. Thus EP<sub>1</sub> antagonists may have potential as a treatment of detrusor overactivity in humans.

**TABLE 1.** Effects of intravenous PF 2907617-02 on cystometric parameters in normal, conscious rats with/without detrusor overactivity induced by intravesical infusion of PGE<sub>2</sub>

	BP	TP	MP	BC	MV	RV	MI
<b>Total Baseline (n=23)</b>	9.5 ± 0.4	24.9 ± 1.2	78.7 ± 6.0	1.22 ± 0.06	1.19 ± 0.06	0.03 ± 0.01	7.17 ± 0.35
<b>1 mg kg<sup>-1</sup> PF 2907617-02 intravenously only (n=5)</b>							
<b>Before</b>	8.7 ± 1.1	22.9 ± 1.0	66.2 ± 6.5	1.29 ± 0.23	1.25 ± 0.22	0.04 ± 0.01	7.53 ± 1.37
<b>After</b>	7.4 ± 1.0 <sup>††</sup>	22.2 ± 1.5 <sup>†</sup>	63.8 ± 6.7 <sup>††</sup>	1.56 ± 0.25* <sup>†</sup>	1.49 ± 0.24* <sup>†</sup>	0.07 ± 0.03	8.91 ± 1.45* <sup>†</sup>
<b>50 uM PGE<sub>2</sub> intravesically only (n=6)</b>							
<b>Before</b>	9.4 ± 0.8	28.4 ± 2.8	93.1 ± 15.6	1.17 ± 0.10	1.12 ± 0.06	0.03 ± 0.01	7.17 ± 0.35
<b>After</b>	12.9 ± 1.1** <sup>††</sup>	36.8 ± 5.0** <sup>†</sup>	137.7 ± 15.3** <sup>††</sup>	0.92 ± 0.06* <sup>†</sup>	0.90 ± 0.06* <sup>†</sup>	0.02 ± 0.01	5.51 ± 0.32* <sup>†</sup>
<b>0.1 mg kg<sup>-1</sup> PF 2907617-02 intravenously and 50 uM PGE<sub>2</sub> intravesically (n=6)</b>							
<b>Before</b>	10.3 ± 1.2	26.3 ± 3.4	87.8 ± 14.9	1.19 ± 0.09	1.17 ± 0.09	0.02 ± 0.01	7.33 ± 0.66

After	12.0 1.0 <sup>‡</sup>	±	28.8 ± 3.4	102.7 17.0	±	0.97 0.09*	±	0.96 0.10	±	0.01 0.00	±	5.84 0.55*	±	
<b>1 mg kg<sup>-1</sup> PF 2907617-02 intravenously and 50 uM PGE<sub>2</sub> intravesically (n=6)</b>														
Before	9.7 ± 0.2		21.9 ± 1.4	65.4 ± 8.3		1.25 0.12	±	1.24 0.11	±	0.02 0.01	±	7.33 0.66	±	
After	9.2 0.4 <sup>††</sup>	±	22.2 1.5 <sup>†</sup>	±	82.5 7.6 <sup>††</sup>	±	1.23 0.11 <sup>†</sup>	±	1.21 0.11 <sup>†</sup>	±	0.02 0.01	±	7.03 0.60 <sup>†</sup>	±

BP: Basal Pressure (cm. H<sub>2</sub>O), TP: Threshold Pressure (cm. H<sub>2</sub>O), MP: Micturition Pressure (cm. H<sub>2</sub>O), BC: Bladder Capacity (ml.), MV: Micturition Volume (ml.), RV: Residual Volume (ml.), MI: Micturition Interval (min.). Results are expressed as mean ± standard error of the mean. Comparisons are made before and after drug administration: \*p < 0.05, \*\*p < 0.01 (paired Student's *t* test), versus the group of 50 uM PGE<sub>2</sub> intravesically only: <sup>†</sup>p < 0.05, <sup>††</sup>p < 0.01 (unpaired Student's *t* test), and versus the group of 1 mg kg<sup>-1</sup> PF 2907617-02 intravenously and 50 uM PGE<sub>2</sub> intravesically: <sup>‡</sup>p < 0.05, <sup>‡‡</sup>p < 0.01 (unpaired Student's *t* test).

**TABLE 2.** Effects of intravenous PF 2907617-02 on cystometric parameters in sham-operated/obstructed, conscious rats.

	BP		TP		MP		BC	MV	RV	MI
	IVP	DP	IVP	DP	IVP	DP				
<b>Sham, intravenous PF 2907617-02 (1 mg./kg.) (n=6)</b>										
<b>Before PF 2907617-02</b>	10.2 ± 0.3	7.4 ± 0.7 <sup>‡‡</sup>	26.9 ± 1.4	18.7 ± 1.4 <sup>‡‡</sup>	73.3 ± 4.7	68.3 ± 4.4	1.66 ± 0.30	1.59 ± 0.32	0.07 ± 0.04	8.63 ± 1.62
<b>After PF 2907617-02</b>	9.7 ± 0.6	7.5 ± 1.0	27.2 ± 1.4	18.8 ± 1.4 <sup>‡‡</sup>	71.8 ± 4.5	67.5 ± 3.8	1.69 ± 0.27	1.57 ± 0.29	0.13 ± 0.07	8.61 ± 1.58
<b>Obstructed, intravenous PF 2907617-02 (1 mg./kg.) (n=6)</b>										
<b>Before PF 2907617-02</b>	9.8 ± 0.6	6.2 ± 1.0 <sup>‡‡</sup>	39.8 ± 6.1	32.8 ± 7.2	72.5 ± 1.0	62.4 ± 8.2	3.08 ± 0.53 <sup>†</sup>	1.38 ± 0.44	1.69 ± 0.61 <sup>†</sup>	15.83 ± 2.86 <sup>†</sup>
<b>After PF 2907617-02</b>	8.5 ± 0.4*	4.6 ± 0.8 <sup>***†‡‡</sup>	35.2 ± 5.4	28.1 ± 5.7	72.5 ± 10.3	59.7 ± 8.6	3.59 ± 0.46 <sup>††</sup>	1.73 ± 0.51	1.86 ± 0.63 <sup>†</sup>	20.62 ± 2.72 <sup>*††</sup>

BP: Basal Pressure (cm. H<sub>2</sub>O), TP: Threshold Pressure (cm. H<sub>2</sub>O), MP: Micturition Pressure (cm. H<sub>2</sub>O), IVP: Intravesical Pressure (cm. H<sub>2</sub>O), DP: Detrusor Pressure, intravesical pressure minus intraabdominal pressure (cm. H<sub>2</sub>O), BC: Bladder Capacity (ml.), MV: Micturition Volume (ml.), RV: Residual Volume (ml.), MI: Micturition Interval (min.). Results are expressed as mean ± standard error of the mean. Comparisons are made before and after drug administration: \*p < 0.05, \*\*p < 0.01 (paired Student's *t* test), between sham and obstructed rats: <sup>†</sup>p < 0.05, <sup>††</sup>p < 0.01 (unpaired Student's *t* test), and between intravesical and detrusor pressure: <sup>‡</sup>p < 0.05, <sup>‡‡</sup>p < 0.01 (paired Student's *t* test)

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