

# Combination of alfuzosin and tadalafil exerts an additive enhancing effect on norepinephrine-induced relaxation of pre-contracted human detrusor smooth muscle

Stephanie Oger<sup>1</sup>, Delphine Bebr-Roussel<sup>1</sup>, Diane Gorny<sup>1</sup>, Thierry Lebret<sup>2</sup>, Pierre Denys<sup>3</sup>, Jacques Bernabé<sup>1</sup>, Francois Giuliano<sup>3</sup>

(1) Pelvipharm, Gif-sur-Yvette, France. (2) Foch Hospital, Suresnes, France. (3) Raymond Poincaré Hospital, Dept. of Neurological Rehabilitation, Garches, France.

PELVI PHARM

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## INTRODUCTION

- Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are highly prevalent in aging men and are strongly linked, independently of age and cardiovascular comorbidities<sup>1</sup>.
- Alpha<sub>1</sub>-adrenergic blockers such as alfuzosin are considered the most effective monotherapy for LUTS associated with benign prostatic hyperplasia (BPH)<sup>2</sup>.
- Phosphodiesterase 5 (PDE5) inhibitors are a first line treatment for erectile dysfunction (ED)<sup>3</sup>.
- Recent clinical trials have shown that PDE5 inhibitors (sildenafil, tadalafil, vardenafil) could improve not only ED but also obstructive and irritative LUTS associated with BPH<sup>4-6</sup>. Interestingly, this beneficial effect on LUTS is not associated with an increased peak flow rate suggesting an extraprostatic mode of action.
- A pilot clinical study also indicates that daily administration of alfuzosin (10mg) in combination with sildenafil (25 mg) for 12 weeks may be more effective than monotherapy on LUTS associated with BPH and ED<sup>7</sup>.
- Tadalafil is currently the only one long-acting PDE5 inhibitor and the maximum prescribed dose (20 mg) shows no clinically relevant hemodynamic interaction with alfuzosin 10mg once daily<sup>8</sup>.

## AIM OF THE STUDY

- We evaluated *in vitro* the effect of alfuzosin, tadalafil or a combination of both drugs on norepinephrine (NE)-induced relaxation of precontracted human detrusor strips.

## MATERIALS & METHODS

### Human detrusor strip preparation

Bladders samples were obtained from 7 patients undergoing cystectomy for bladder cancer with no history of bladder dysfunction. Serosal and mucosal layers were removed from bladder samples, and detrusor strips were mounted in 5 ml organ baths filled with Krebs-HEPES buffer maintained at 37°C and continuously bubbled with 95%O<sub>2</sub>-5%CO<sub>2</sub>. The strips were connected to force transducers for isometric tension recordings (Pioden Controls Ltd, UK). Following amplification, the tension changes were computerized via MacLab™/8 using Chart™ 5 software (AD Instruments Ltd).



### In vitro contractile experiments

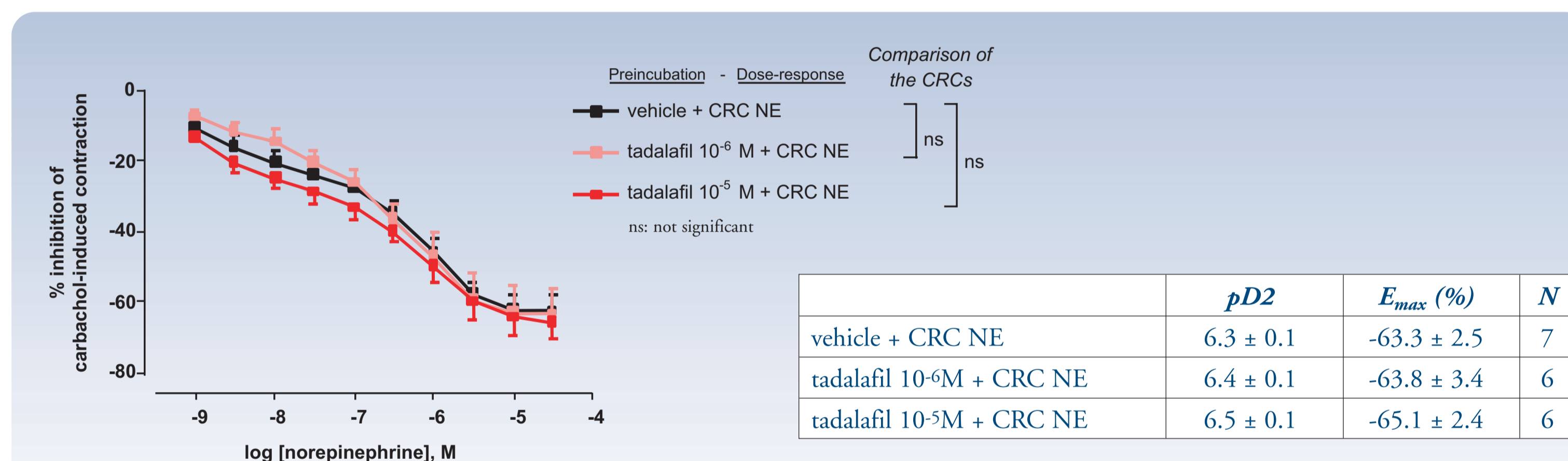
Strips were exposed to carbachol (10<sup>-6</sup>M, 10 minutes) followed by NE (10<sup>-5</sup>M, 10 minutes) to evaluate their contractile and relaxant capacity. Then strips were incubated for 20-minute period with alfuzosin (at two different concentrations: 10<sup>-6</sup> and 10<sup>-5</sup>M) or tadalafil (at two different concentrations: 10<sup>-6</sup> and 10<sup>-5</sup>M) or two combinations of both compounds (alfuzosin 10<sup>-6</sup>M + tadalafil 10<sup>-6</sup>M and alfuzosin 10<sup>-5</sup>M + tadalafil 10<sup>-5</sup>M) or vehicle. Strips were then pre-contracted with carbachol (10<sup>-6</sup>M) and allowed to re-equilibrate until a stable response was obtained (≈ 20 minutes). Then, a concentration response curve (CRC) to NE (10<sup>-9</sup>M to 3.10<sup>-5</sup>M) was performed.

### Data Analysis

Results were expressed as a percentage of inhibition of the contractile response to carbachol. For each CRC in presence of vehicle or alfuzosin or tadalafil or combination of both, a pD<sub>2</sub> value (-log concentration of compound that produces 50 % reduction of the maximal response) and a mean maximal effect (E<sub>max</sub>) were evaluated. Data were expressed as mean ± SEM for N experiments corresponding to N detrusor samples. Statistical analysis was performed according to the extra sum of squares F test principle with GraphPad Prism® 4.03 software.

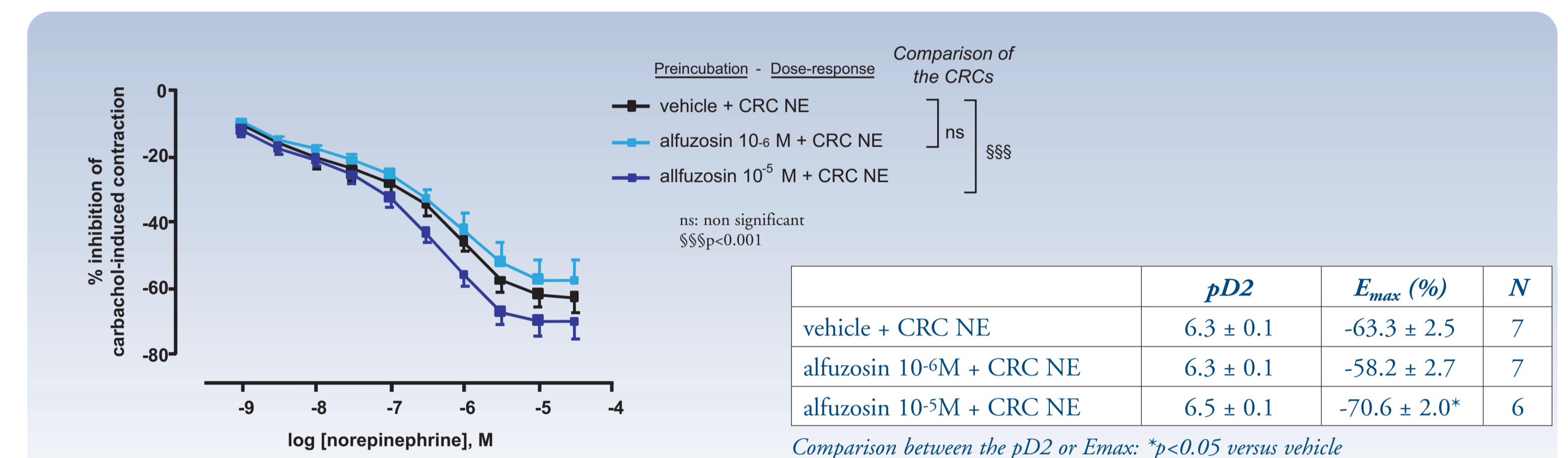
## RESULTS

### Effect of tadalafil on the relaxation induced by NE on carbachol pre-contracted human detrusor strips



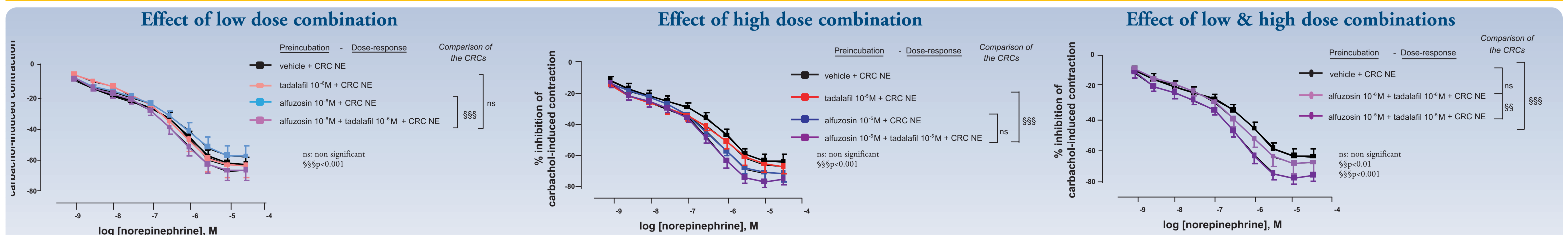
- Tadalafil from 10<sup>-6</sup> to 10<sup>-5</sup>M does not enhance NE-induced relaxation of carbachol pre-contracted detrusor strips

### Effect of alfuzosin on the relaxation induced by NE on carbachol pre-contracted human detrusor strips



- Alfuzosin (10<sup>-5</sup>M) enhances the relaxant effect of NE on carbachol pre-contracted detrusor strips

### Effect of the combination of tadalafil and alfuzosin on the relaxation induced by NE on carbachol pre-contracted human detrusor strips



	pD <sub>2</sub>	E <sub>max</sub> (%)	N
tadalafil 10 <sup>-6</sup> M + CRC NE	6.4 ± 0.1	-63.8 ± 3.4	6
alfuzosin 10 <sup>-6</sup> M + CRC NE	6.3 ± 0.1	-58.2 ± 2.7	7
tadalafil 10 <sup>-6</sup> M + alfuzosin 10 <sup>-6</sup> M + CRC NE	6.5 ± 0.1	-66.8 ± 2.8*	7

Comparison between the pD<sub>2</sub> or E<sub>max</sub>: \*p<0.05 versus alfuzosin 10<sup>-6</sup>M

	pD <sub>2</sub>	E <sub>max</sub> (%)	N
tadalafil 10 <sup>-5</sup> M + CRC NE	6.5 ± 0.1	-65.1 ± 2.4	6
alfuzosin 10 <sup>-5</sup> M + CRC NE	6.5 ± 0.1	-70.6 ± 2.0*	6
tadalafil 10 <sup>-5</sup> M + alfuzosin 10 <sup>-5</sup> M + CRC NE	6.5 ± 0.1	-75.9 ± 2.2**	7

Comparison between the pD<sub>2</sub> or E<sub>max</sub>: \*p<0.05, \*\*p<0.01 versus tadalafil 10<sup>-5</sup>M

	pD <sub>2</sub>	E <sub>max</sub> (%)	N
vehicle + CRC NE	6.3 ± 0.1	-63.3 ± 2.5	7
tadalafil 10 <sup>-6</sup> M + alfuzosin 10 <sup>-6</sup> M + CRC NE	6.5 ± 0.1	-66.8 ± 2.8	7
tadalafil 10 <sup>-5</sup> M + alfuzosin 10 <sup>-5</sup> M + CRC NE	6.5 ± 0.1	-75.9 ± 2.2***#	7

Comparison between the pD<sub>2</sub> or E<sub>max</sub>: \*\*\*p<0.001 versus vehicle; #p<0.05 versus tadalafil 10<sup>-6</sup>M + alfuzosin 10<sup>-6</sup>M

- The combination of tadalafil and alfuzosin further enhances the inhibitory effect of NE on carbachol-induced contractions of human detrusor strips compared to each compound alone

## CONCLUSIONS

- Alfuzosin and tadalafil show *in vitro* an additive enhancing effect on the relaxation induced by norepinephrine on carbachol pre-contracted human detrusor.
- These experiments provide experimental support for the clinical investigation of the combination of α<sub>1</sub>-blockers and PDE5 inhibitors in the treatment of LUTS associated with BPH and possibly overactive bladder.