Abstract n°56: COMPARISON OF THE EFFECTS OF BESIPIRDINE, ITS MAIN METABOLITE AND DULOXETINE ON URETHRAL PRESSURE IN ANESTHETIZED FEMALE RATS.

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INTRODUCTION & OBJECTIVES

- Besipirdine (BES) is currently undergoing clinical trials in Europe and Australia in patients suffering from overactive bladder.
- BES is a norepinephrine (NE) reuptake inhibitor whereas its main metabolite, HP748, is a partial agonist of the α_1-adrenoceptor subtype (1) in rabbit isolated urethra.
- Since adrenergic innervation is known to be implicated in maintaining urethral pressure in humans, the aims of the present study were to evaluate the effects of BES (0.1-3 mg/kg i.v.) and HP748 (0.01-0.3 mg/kg i.v.) on urethral pressure (UP) in rats. Results were compared to the effects of duloxetine (DLX; 0.1-3 mg/kg i.v.), a balanced NE and serotonin reuptake inhibitor.

MATERIALS & METHODS

- In anesthetized female Wistar rats, the urethra was catheterized *via* the bladder base. Saline was infused into the urethra (0.5 mL/h) and UP was continuously recorded. After a stabilization period of 20 minutes (basal UP), four consecutive doses of BES, HP748, DLX or their vehicle (NaCl 0.9%) were given intravenously (1 minute perfusion) at 20 minutes intervals. The maximal increase in UP after each dose was expressed as percentage of variation from the value before each administration (basal values). $UP_{25\%}$ and $UP_{50\%}$ were then calculated by linear regression. Results are given as mean ± sem.

BASAL URETHRAL PRESSURE

- Basal UP was not statistically different between groups (ANOVA one-way, p> 0.05; Table 1).

EFFECTS OF VEHICLE ON URETHRAL PRESSURE

- Four consecutive administrations of vehicle did not modify significantly UP (Figure 1).

EFFECTS OF BESIPIRDINE, HP748 AND DULOXETINE ON URETHRAL PRESSURE

- All tested compounds significantly increased UP. The effects of BES and HP748 were dose-dependent and maximal effects were observed at 3 and 0.3 mg/kg, respectively (Figure 1). In contrast, the effects of DLX were not dose-dependent and the maximal effect was observed at 0.3 mg/kg. For each group, $UP_{25\%}$ and $UP_{50\%}$ are reported on Table 1.

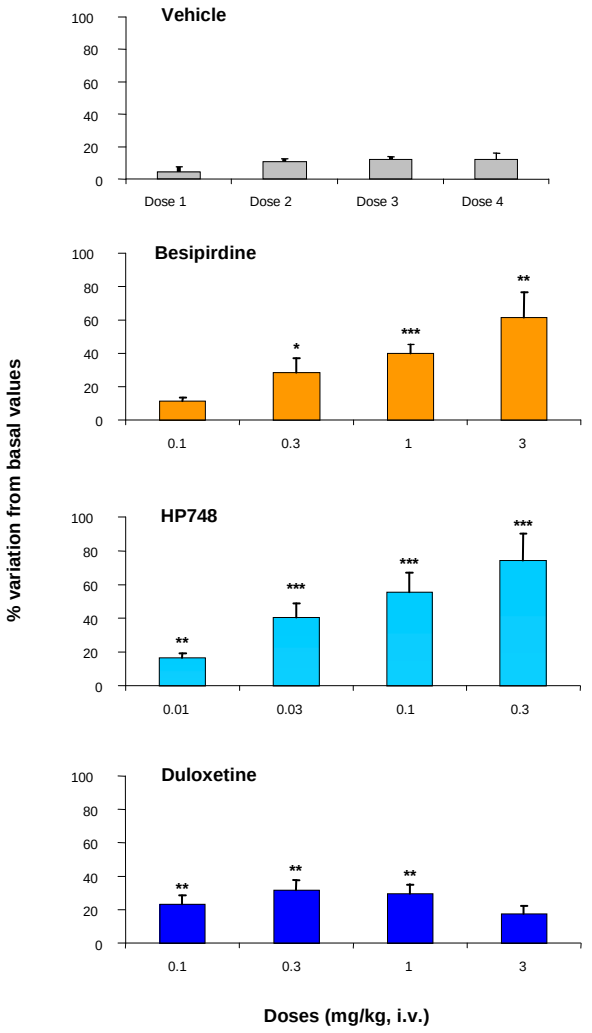
Table 1: ***Effects of vehicle (NaCl 0.9%), besipirdine, HP748 and duloxetine (i.v.) on urethral pressure in anesthetized female rats.***

Compounds	Basal UP (mmHg)	Maximal Observed Effects (%)	$UP_{25\%}$ (mg/kg)	$UP_{50\%}$ (mg/kg)
Vehicle	8.9±0.7	12.3±3.6	-	-
Besipirdine	8.4±0.8	61.5±15.2*	0.47±0.13$^{\#}$	0.84±0.21
HP748	9.8±0.9	74.2±16.7*	0.03±0.01$^{\#\#}$	0.12±0.04
Duloxetine	10.2±0.7	31.8±5.9*	0.13±0.03	-

* p< 0.05 *vs* vehicle-treated rats, unpaired Student *t*-test.
$^{\#}$ p< 0.05 ; $^{\#\#}$ p< 0.01 *vs* duloxetine-treated rats, unpaired Student *t*-test.

$UP_{x\%}$: dose increasing basal UP by X%. n=8 per group

Figure 1: ***Effects of vehicle (NaCl 0.9%), besipirdine, HP748 and duloxetine on urethral pressure in anesthetized female rats.***



* p< 0.05; ** p< 0.01; ***p< 0.001 *vs* vehicle-treated rats, unpaired Student *t*-test.

DISCUSSION

- In anesthetized female rats, BES, HP748 and DLX increased UP. The maximum observed effects were much higher with BES and HP748 than with DLX.
- Based on maximal effects, $UP_{25\%}$ and $UP_{50\%}$, the rank order of potency is:

  HP748 > BES > DLX
- Potentiation of the noradrenergic tonus at the urethral level through NE reuptake inhibition may explain the effects of BES and DLX since it has been demonstrated that BES at 1 µM potentiated the concentration response curve to norepinephrine in rabbit isolated urethra (1). Moreover venlafaxine, a selective NE reuptake inhibitor was reported to increase UP in rats (2).
- HP748 effects are similar to those observed with phenylephrine in anesthetized rats (3) and consistent with its α_1-adrenoceptor agonist activity (1).

CONCLUSION

We conclude that besipirdine, by itself and through the activity of its main metabolite (HP748), could be useful to treat stress or mixed urinary incontinence in humans.

REFERENCES

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