56

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COMPARISON OF THE EFFECTS OF BESIPIRDINE, ITS MAIN METABOLITE AND DULOXETINE ON URETHRAL PRESSURE IN ANESTHETIZED FEMALE RATS

Hypothesis / aims of study

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). Adrenergic innervation is known to be implicated in maintaining urethral pressure in humans. Therefore, we evaluated the effects of BES (0.1-3 mg/kg iv) and HP748 (0.01-0.3 mg/kg iv) in comparison to duloxetine (DLX; 0.1-3 mg/kg iv), a balanced NE and serotonin reuptake inhibitor, on urethral pressure (UP) in rats.

Study design, materials and 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 20-min stabilization period (basal values), 4 consecutives doses of BES, HP748, DLX or their vehicle (NaCl 0.9%) were given intravenously (1-min 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. $UP_{25\%}$ and $UP_{50\%}$ were then calculated by linear regression. Results are given as mean ± sem.

Results

Basal UP was not statistically different between groups (ANOVA one-way, $p>0.05$; Table). In comparison to vehicle, 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 (Table). 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 the table.

Interpretation of results

In anesthetized rats, BES, HP748 and DLX increased UP with the following rank order of potency: HP748 > BES > DLX. The maximum observed effects were much higher with BES and HP748 than with DLX. Potentiation of the noradrenergic tonus at the urethral level through NE reuptake inhibition may explain the effects of BES and DLX since BES at 1 µM potentiated the concentration response curve to norepinephrine in rabbit isolated urethra (1). Moreover venlafaxine, a selective NE reuptake inhibitor increased UP in rats (2). In contrast, HP748 effect is similar to that of phenylephrine (3) and consistent with its α_1-adrenoceptor agonist activity.

Concluding message

We conclude that BES, by itself and through the activity of its metabolite, could be useful to treat stress urinary incontinence in humans.

References

1. Neurourol Urodyn (2006) 25; 585-86
2. BJU Int (2001) 88 ; 771-775
3. Life Sci (1998) 63; 169-176

Table

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

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