

Abstract n°249: CHRONIC TREATMENT WITH BESPIRIDINE INCREASED BLADDER CAPACITY IN CONSCIOUS FEMALE RATS SUBJECTED TO BLADDER OUTLET OBSTRUCTION – RELATIONSHIP WITH PLASMA CONCENTRATION.

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INTRODUCTION & OBJECTIVES

- Besipirdine (BES), a norepinephrine (NE) reuptake inhibitor (1, 2), is currently undergoing clinical trials in Europe and Australia in patients suffering from overactive bladder.
- Chronic Bladder Outlet Obstruction (BOO) in female rats is a well known experimental model of bladder dysfunctions (3).
- The aim of the present study was to evaluate the effects of a chronic treatment (7 days s.c.) with BES (1, 3 and 10 mg/kg/day), on BOO-induced bladder dysfunctions and to determine its plasmatic concentrations.

MATERIALS & METHODS

Animals

- BOO was performed as previously described (3). In female Wistar rats under isoflurane anesthesia, a ligature was tied around the urethra leaving a 1 mm diameter lumen.
- Five weeks later, Alzet[®] osmotic pumps filled with BES or vehicle (NaCl 0.9%) were implanted subcutaneously in the obstructed (OBS) rats. After a 7 day-treatment under isoflurane anesthesia, the osmotic pump and the ligature were removed and a catheter implanted in the bladder.

Cystometric investigations

- Cystometric investigations were performed two days after bladder catheterization in conscious animals.
- Bladder was perfused (NaCl 0.9%, 10 mL/h) and 5 micturition cycles were performed for each animal. Results are given as mean values \pm sem.
- Threshold Pressure (ThP), Micturition Pressure (MP), Basal Pressure (BP) and Bladder Capacity (BC) were analyzed.
- In separate rats and in order to measure plasmatic concentration of BES, blood samples were collected at the end of the treatment and BES assayed using a validated LC-MS/MS method.

RESULTS

- BOO induced alterations in micturition patterns as previously described (3) (data not shown).
- In comparison to its vehicle, BES at 10 mg/kg/day induced a significant (3.5 fold) increase in BC (Figure 1A) whereas no statistical significant effect was observed at 1 and 3 mg/kg/day.
- BES, produced a dose-dependent increase in plasma levels, the maximal being 508 \pm 141 ng/mL in the 10 mg/kg/day group (Figure 1B).
- No significant effect was observed on ThP, MP and BP (Table 1).

Figure 1: Effects of chronic besipirdine treatment (7 days s.c.) in rats with Bladder Outlet Obstruction.

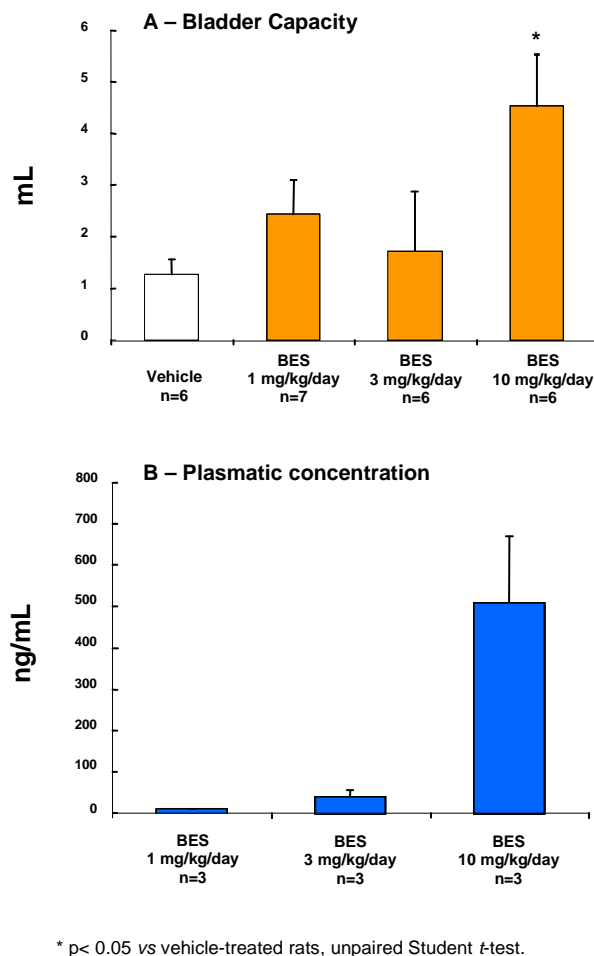


Table 1: Effects of vehicle and besipirdine on cystometric parameters in conscious rats with BOO.

Compounds	ThP (mmHg)	MP (mmHg)	BP (mmHg)
Vehicle n=6	13.1 \pm 1.7	27.9 \pm 2.7	6.9 \pm 0.3
BES (1 mg/kg/day) n=7	12.9 \pm 0.7	34.0 \pm 5.6	6.2 \pm 0.4
BES (3 mg/kg/day) n=7	11.4 \pm 1.1	31.9 \pm 5.5	7.4 \pm 1.8
BES (10 mg/kg/day) n=7	14.6 \pm 0.8	35.9 \pm 4.6	8.6 \pm 2.4

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

REFERENCES

1. Smith CP *et al.* CNS Drug Reviews 3: 1-23, 1997.
2. Palea S *et al.* NeuroUrol Urodyn 25: 585-86, 2006.
3. Lluel P *et al.* J Urol, 60: 2253-2257, 1998.
4. Bae JH *et al.* BJU Int 88: 771-5, 2001.

DISCUSSION

- Chronic treatment with BES at 10 mg/kg/day significantly increased BC. This effect was not associated with an effect on bladder contractility, since BES was without effect on MP. Similarly, bladder compliance was unaffected as reflected by the lack of effect on BP and ThP.
- BES has high affinity for the rat NE transporter (IC_{50} = 100 nM, 1) and induced a statistically significant potentiation of the concentration response curve to norepinephrine in the rabbit isolated urethra at 1 μ M (2).
- Since the plasma concentration of BES administered at 10 mg/kg/day s.c. corresponds to 1.74 μ M, we propose that the effect on BC could be due to a potentiation of the noradrenergic tonus at the urethral level as previously described in anesthetized rats using venlafaxine, a selective NE reuptake inhibitor (4).

CONCLUSION

Taken together these results suggest that besipirdine could be useful to treat patients suffering of urinary incontinence or lower urinary tract symptoms (LUTS).