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CHRONIC TREATMENT WITH BESIPIRDINE INCREASED BLADDER CAPACITY IN CONSCIOUS FEMALE RATS SUBJECTED TO BLADDER OUTLET OBSTRUCTION – RELATIONSHIP WITH PLASMA CONCENTRATION

Hypothesis / aims of study

Besipirdine (BES) is currently undergoing clinical trials in Europe in patients suffering from overactive bladder. Chronic Bladder Outlet Obstruction (BOO) in female rats is a well known experimental model of bladder dysfunctions. 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 concentration.

Study design, materials and methods

In female Wistar rats 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, the osmotic pump and the ligature were removed and a catheter implanted in the bladder. Cystometric investigations were performed two days later in conscious animals. Bladder was perfused (NaCl 0.9%,10 mL/h) and 5 micturition cycles were performed for each animal. Micturition pressure (MP), Basal Pressure (BP), Threshold Pressure (ThP) and Bladder Capacity (BC) were analyzed. In separate rats, blood samples were collected at the end of the treatment and HP749 assayed using a validated LC-MS/MS method.

Results

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 for this parameter. No significant effect was observed on MP, ThP and BP. Assayed in separated groups, BES, produced a dose-dependent increase in plasma levels, the maximal being 508±141 ng/mL in the 10 mg/kg/day group (Figure 1B).

Interpretation of results

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} = 100nM, 1) and induced a statistically significant potentiation of the concentration response curve to norepinephrine in the rabbit isolated urethra at 1µM (2). Since the plasma concentration of BES administrated at 10 mg/kg/day s.c. corresponds to 1.74 µM, 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 (3).

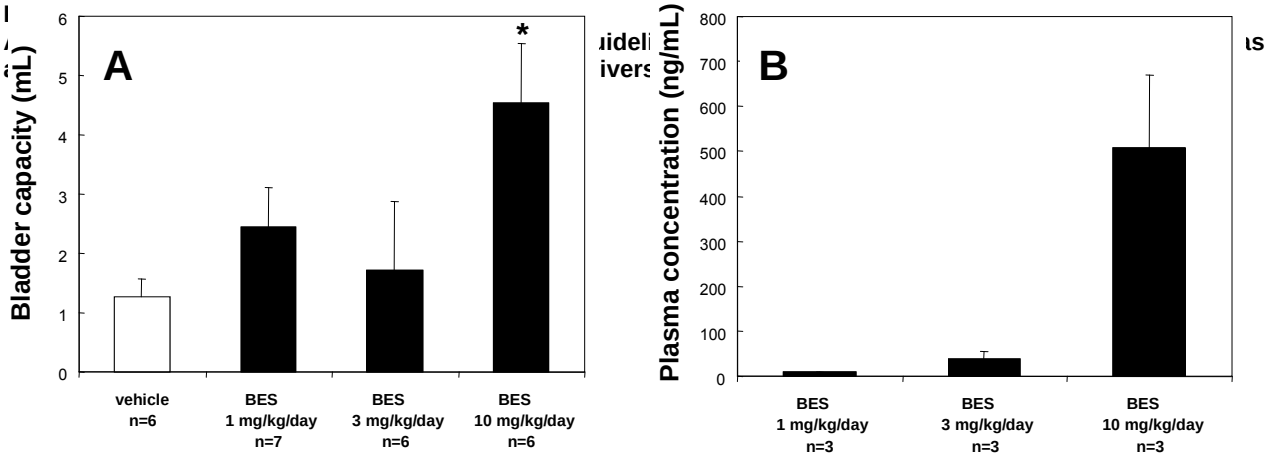
Concluding message

Taken together these results suggest that BES could be useful to treat patients suffering of urinary incontinence.

References

1. CNS Drug Reviews (1997) 3; 1-23
2. Neurourol Urodyn (2006) 25; 585-86
3. BJU Int (2001) 88 ; 771-5

Effects of chronic BES treatment (7 days s.c.) in rats with Bladder Outlet Obstruction
(A) Bladder capacity; (B) Plasma concentration



* p<0.05 vs vehicle treated rat, Unpaired t test