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EFFECTS OF LITOXETINE ON TWO IN VIVO EXPERIMENTAL MODELS OF MIXED URINARY INCONTINENCE

Hypothesis / aims of study:
Litoxetine (LTX) is a highly selective serotonin (5-HT) reuptake inhibitor and a Multifunctional Serotonin Agonist Antagonist (1, 2). LTX is currently in phase 2 development in an international multicenter clinical trial for the treatment of Mixed Urinary Incontinence (MUI) in women. 5-HT plays an important role in centrally and peripherally modulating the reflexes of continence/micturition; 5-HT potentiates the guarding reflex which allows continence by increasing urethral pressure and inhibiting micturition reflex.
The aims of this preclinical study were to determine the effects of LTX in two *in vivo* experimental models of MUI. In rats, the effects of LTX were evaluated on bladder and urethral functions. In rabbits, LTX was evaluated in comparison to duloxetine (DLX) on striated anal sphincter functions in a model of detrusor overactivity. The external anal sphincter serves as a proxy of urethral sphincter activity.

Study design, materials & methods:
Rat experiments: In anesthetized female rats, the urethra or the bladder were catheterized. Saline was infused into the urethra (0.5 mL/h) and Urethral Pressure (UP) was continuously recorded. After a stabilization period (basal values), a single dose of LTX (0.1, 0.3, 1 or 2 mg/kg) or vehicle were given intravenously (i.v.) and UP was recorded for 1 hour. Maximal increase in UP was calculated in each group. Cystometric investigations were performed in separate anesthetized female rats. Physiological saline or 0.3% acetic acid (AA) was infused into the bladder at a constant flow rate (3 mL/h). After a stabilization period (basal values), LTX (2 mg/kg) or vehicle, were administered i.v. and vesical pressure was recorded for 1 hour. Micturition pressure (MP), basal pressure (BP), threshold pressure (ThP) and bladder capacity (BC) were analyzed.

Rabbit experiments: A total of 24 female halothane-anaesthetized rabbits under irritated conditions (continuous bladder infusion of 0.5% AA) were used. Cumulative doses of vehicle, LTX or DLX (1 and 3 mg/kg) were administered i.v. in a time-matched manner and their effects on bladder capacity (BC), micturition volume (MV), residual volume (RV), basal pressure (BP), contraction duration (CD), intercontraction interval (ICI) and contraction amplitude (CA) were measured. Simultaneously, electromyographic activity of the striated anal sphincter (SAS-EMG) was recorded. Vehicle, LTX and DLX effects were analyzed and compared with stabilization period values.

Results:
Rat experiments: UP measurement (Fig.1A). Basal UP was not statistically different between groups. Following administration of vehicle small variations of UP were observed. In contrast, LTX induced a dose-dependent increase of UP. In comparison to vehicle, LTX effects were significant starting from the dose of 0.3 mg/kg.
Cystometry (Fig.1B). In animals with intravesical AA infusion, ThP and BC were markedly and significantly decreased in comparison to saline infused animals (data not shown). No significant difference was observed for all other cystometric parameters. In rats infused with AA, LTX (2 mg/kg, i.v.) significantly increased BC during the 60 min observation period (Fig. 1B). At this dose, LTX was devoid of significant effect on MP, BP and ThP.

Rabbit experiments: Intravesical infusion of AA induced reproducible micturition patterns. Vehicle administration did not affect BC (Fig. 2A). On SAS-EMG activity (Fig. 2B), the first administration of vehicle was without effect whereas a decrease occurred after the second administration. At 1 mg/kg, LTX did not modify either BC or SAS-EMG activity. In contrast, at 3 mg/kg, LTX significantly increased BC and SAS-EMG activity. At 1 and 3 mg/kg, DLX dose-dependently and significantly increased BC and SAS-EMG activity. DLX also significantly increased MV at 3 mg/kg (data not shown). LTX and DLX were devoid of significant effects on the other cystometric parameters analyzed (data not shown).

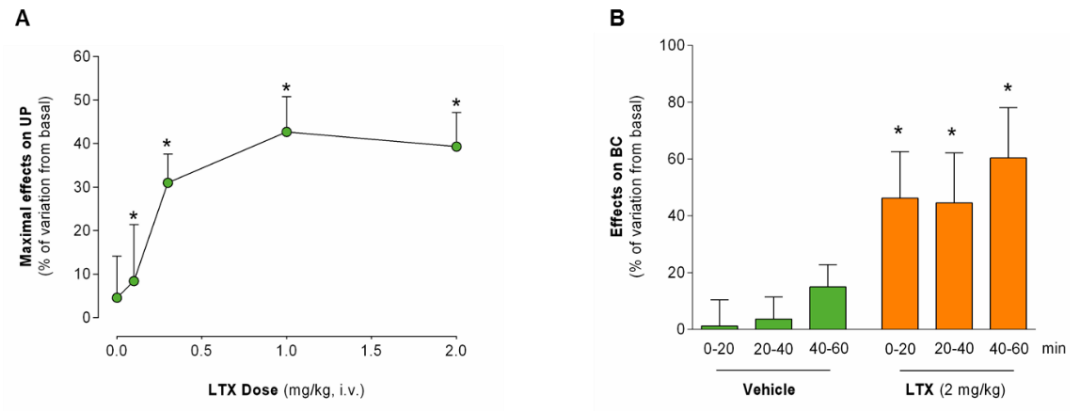

Fig. 1: Effects of LTX in anesthetized female rats on (A) urethral pressure and (B) bladder capacity with intravesical AA infusion. Data represent mean values ± SEM, * $p < 0.05$.

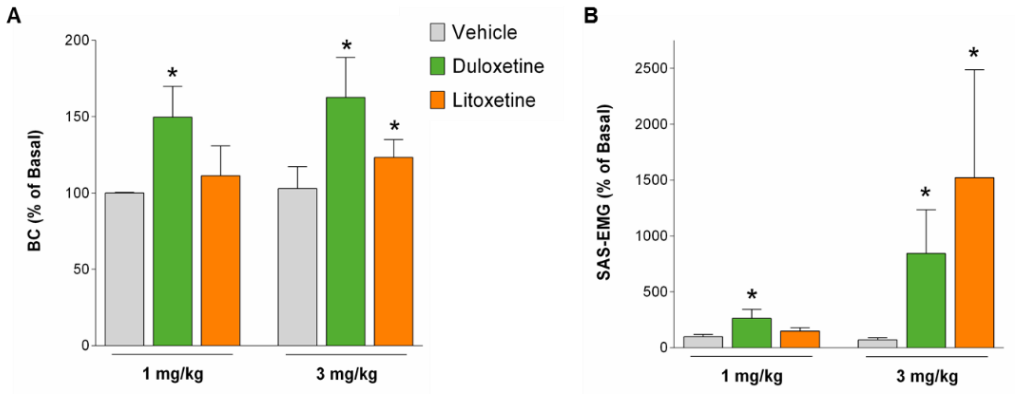

Fig. 2: Effects of LTX on (A) bladder capacity and (B) SAS-EMG in anesthetized female rabbits with intravesical AA infusion. Data represent mean values ± SEM, * $p < 0.05$.

Interpretation of Results:

We showed that LTX increased UP, BC and striated sphincter activity. Considering the pharmacological profile of LTX, it could be proposed that these effects could be related to a 5-HT-mediated mechanism involving spinal or supraspinal structures, as reported for duloxetine (3). However, a direct effect on bladder and/or urethral smooth muscles cannot be ruled out.

Concluding message

These data support the therapeutic potential of litoxetine as a new treatment of mixed urinary incontinence.

References

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Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** rats and rabbits **Ethics Committee:** Experiments were performed in accordance with European directives