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EFFECTS OF LITOXETINE ON ACETIC ACID-INDUCED DETRUSOR OVERACTIVITY AND STRIATED ANAL SPHINCTER FUNCTIONS IN RABBITS: COMPARISON WITH DULOXETINE

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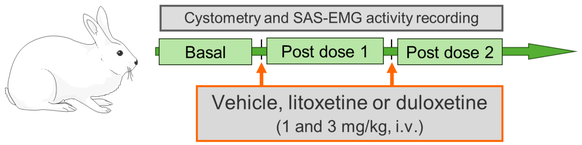
Objectives

Litoxetine (LTX) is a highly selective serotonin (5-HT) reuptake inhibitor and a Multifunctional Serotonin Agonist Antagonist [1,2]. The aim of this study was to characterize the effects of LTX, in comparison to duloxetine (DLX), a non-selective norepinephrine (NE)/5-HT reuptake inhibitor, on both detrusor and striated anal sphincter functions in a rabbit model of detrusor overactivity [3]. The external anal sphincter model was used as a proxy of urethral sphincter activity [4].

Methods

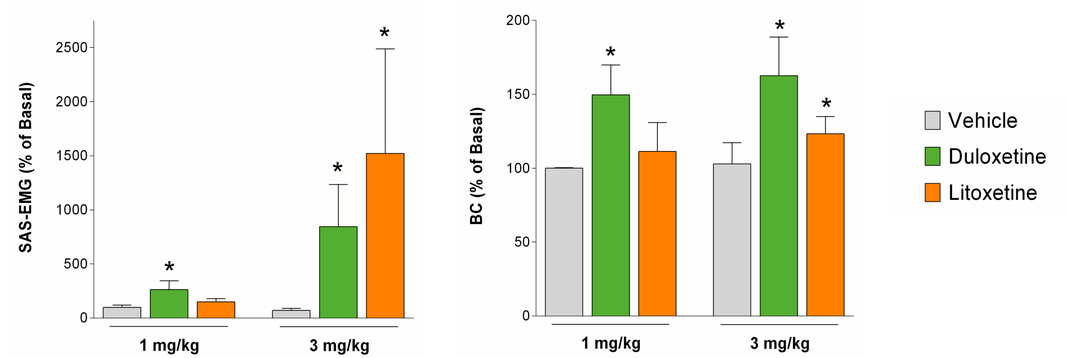
- **Animals:** Female New Zealand white rabbits (~3 kg).
- **Surgery:** Under halothane-anesthesia, a catheter was inserted in the bladder through the dome and secured with a purse-string suture. Two electrodes were inserted into the striated anal sphincter (SAS)
- **Cystometry** was performed in halothane-anesthetized animals with continuous intravesical infusion of 0.5% acetic acid (AA)
- **Treatments:** In each animal, two successive intravenous administrations of vehicle or two doses of LTX or DLX (1 and 3 mg/kg) were performed in a time-matched manner and their effects on bladder capacity (BC), micturition volume (MV), residual volume (RV), baseline pressure (BP), contraction duration (CD), intercontraction interval (ICI) and contraction amplitude (CA) were measured.
- **Bladder Pressure and Striated anal sphincter electromyographic (SAS-EMG) activity** were recorded simultaneously.

Vehicle, LTX and DLX effects were analyzed and compared with stabilization period (basal values) using Wilcoxon rank test.



Results

- Intravesical infusion of AA induced reproducible micturition patterns. BC and ICI were lower than in animals with infusion of saline, confirming the induction of bladder overactivity. No effect was observed on all other cystometric parameter studied (data not shown).



Data represent mean values ± SEM (n=7-8/group). * p < 0.05, Wilcoxon rank test *vs* stabilization period (SP)

- Vehicle administration did not affect cystometric parameters. On SAS-EMG activity, the first administration of vehicle was without effect whereas a significant decrease (-70±19%) occurred after the second administration.
- At 1 mg/kg, LTX did not significantly modify either cystometric parameters or SAS-EMG activity. In contrast, at 3 mg/kg, LTX significantly increased BC (123±12%) and SAS-EMG activity (1522±967%).
- DLX dose-dependently and significantly increased BC (150±20% and 163±26% at 1 and 3 mg/kg, respectively) and SAS-EMG activity (262±81% and 844±390% at 1 and 3 mg/kg, respectively). DLX also significantly increased MV at 3 mg/kg (146±14%, data not shown).
- LTX and DLX were devoid of significant effects on the other cystometric parameters.

Conclusions

LTX significantly reduced bladder hyperactivity, resulting in increased bladder capacity, while simultaneously increasing splinter activity. At the dose of 3 mg/kg, the effects of LTX and DLX were similar.

The current results support that LTX could be useful for treating lower urinary tract dysfunctions such as mixed urinary incontinence.

References

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