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EFFECTS OF BESIPIRDINE ON ACETIC ACID-INDUCED BLADDER IRRITATION IN RABBITS. COMPARISON WITH DULOXETINE.

Hypothesis / aims of study

Besipirdine is a new drug under clinical investigation for the treatment of OAB. It combines monoamine reuptake inhibition and interaction at alpha1 (agonist) and alpha2 (antagonist) receptors.
The study aimed at characterizing the effects of besipirdine on both detrusor and striated sphincter functions in a rabbit model of bladder overactivity. In order to validate the model and compare the results, duloxetine, a non-selective NE / 5-HT reuptake inhibitor, was included in the study.

Study design, materials and methods

A total of 24 female halothane-anaesthetized rabbits under irritated conditions (continuous bladder infusion of 0.5% acetic acid) were used for the experiment. Cumulative doses of HP-749 (0, 1, 3 and 5 mg/kg), or duloxetine (0, 1 and 2 mg/kg) were administered intravenously 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. Simultaneously, electromyographic activity of the striated urethral sphincter (SS-EMG) was recorded. Results were analysed and compared with control values using Wilcoxon rank test. Mann-Whitney U test was performed to compare the effects of duloxetine and besipirdine.

Results

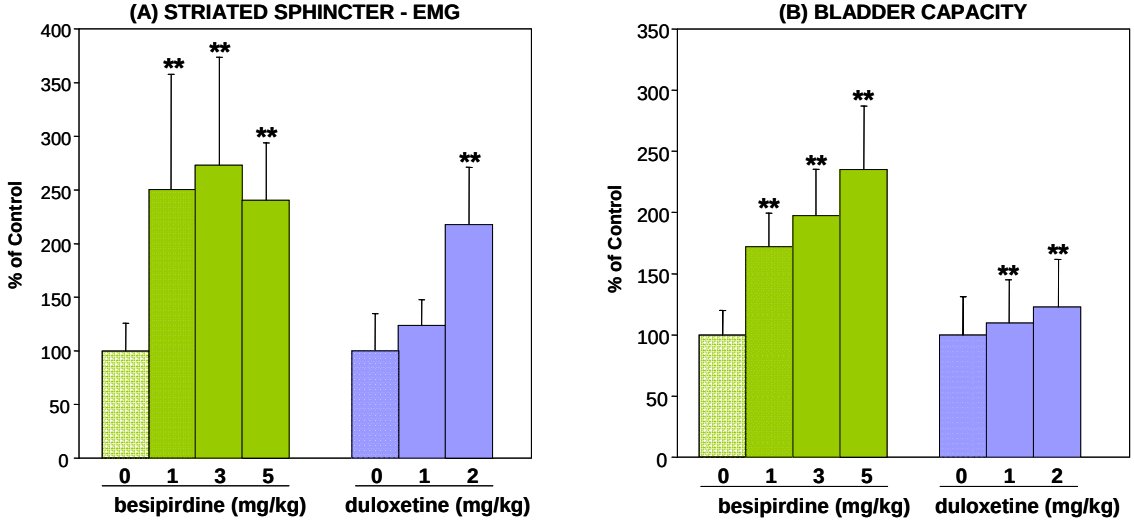
With continuous infusion of acetic acid in the bladder, reproducible micturition patterns were obtained. BC and ICI were lower than with infusion of saline, confirming the induction of bladder overactivity (data not shown).
Differences in the electromyographic and cystometric parameters between the initial administration of vehicle (saline) and subsequent administration of the drugs were observed.

1. Under irritated conditions, iv administration of 1 mg/kg duloxetine had a slight but statistically significant effect on bladder capacity, ICI, and micturition volume (110%, 128% and 187%, respectively; Figure 1B) as compared to control values (iv saline administration). The effects were higher with the subsequent administration of 2 mg/kg iv. At this dose, a marked increase (219%) in striated sphincter EMG activity was observed (Figure 1A). The contraction amplitude was not affected by duloxetine, the contraction duration being slightly but significantly increased (130% at 2 mg/kg).

2. Intravenous administration of 1 mg/kg besipirdine resulted in a marked increase in striated sphincter EMG activity (250%). Bladder capacity, ICI and micturition volume were also increased (172%, 208% and 136% respectively) as compared to saline administration (Figure 1B).
Consecutive administration of 3 and 5 mg/kg besipirdine resulted in a dose-dependent increase in these cystometric parameters. On striated sphincter EMG, the highest effect was observed after 3 mg/kg (273%; Figure 1A). As with duloxetine, contraction amplitude was not affected by besipirdine.

3. Besipirdine and duloxetine displayed similar effects on striated sphincter and detrusor functions. In this model, besipirdine appeared more potent than duloxetine. At the dose of 1 mg/kg, the effects of besipirdine were significantly higher on striated sphincter EMG, bladder capacity and ICI than those observed after the cumulative administration of 1 and 2 mg/kg duloxetine. Thus, at 1 mg/kg, the increase in EMG activity was twice as high with besipirdine as with duloxetine ($p < 0.05$; Mann-Whitney U test). Besipirdine was also significantly more potent than duloxetine ($p < 0.05$) on bladder capacity and ICI. There were no significant differences in micturition volume between drugs.

Figure 1: Effect of besipirdine and duloxetine on striated sphincter EMG (A) and Bladder capacity (B)



Interpretation of results

In this rabbit model, duloxetine increased the striated sphincter EMG activity and the bladder capacity of the striated sphincter, confirming earlier results obtained in the same model (1). Similar results were obtained both in a cat model and in the clinics in women (2,3). This indicates that the rabbit model of bladder overactivity is suitable to study the effect of drugs on the lower urinary tract.

Besipirdine also effectively reduced bladder irritation, markedly increasing external urethral sphincter activity, bladder capacity and decreasing the frequency of micturition contractions. In this model, besipirdine appeared much more potent than duloxetine. At the lowest tested dose (1 mg/kg), the effect on striated sphincter EMG appeared to have reached a maximum.

Duloxetine acts centrally at Onulf's nucleus to facilitate sphincter activity during urine storage. The similar profiles of besipirdine and duloxetine in this rabbit model suggest that besipirdine also acts, at least in part, on the central nervous system.

Concluding message

Overall, besipirdine potentiated urethral activity and reduced bladder irritation in New Zealand White rabbits. In this model, it was more potent than duloxetine, a drug currently approved for the treatment of stress urinary incontinence.
The data support the potential of besipirdine as a new treatment for lower urinary tract dysfunctions such as stress urinary incontinence or OAB.

References

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FUNDING: **NONE**
DISCLOSURES: **NONE**
ANIMAL SUBJECTS: **This study followed the guidelines for care and use of laboratory animals and was approved by Helsinki declaration**