129

Palea S[1], Guilloteau V[1], Guerard M[1], Guardia Llorens M[1], Cantoreggi S[2], Lovati E[2], Pietra C[2], Lluel P[1]
1. *UROsphere, Faculty of Pharmaceutical Sciences, 35 Chemin des Maraîchers, 31062 Toulouse Cedex 09, France,* ***2.*** *Helsinn SA, Research & Development, Lugano, Switzerland*

COMPARISON OF THE EFFECTS OF NETUPITANT AND TOLTERODINE ON OVERACTIVE BLADDER INDUCED BY INTRAVESICAL ACETIC ACID INFUSION IN ANESTHETIZED FEMALE GUINEA-PIGS.

Hypothesis / aims of study

The aim of this study was to evaluate the effects of netupitant (a selective NK_1 receptor antagonist) and tolterodine (a muscarinic receptor antagonist) on cystometric parameters in acetic acid (AA)-induced overactive bladder (OAB) in anesthetized female guinea-pigs.

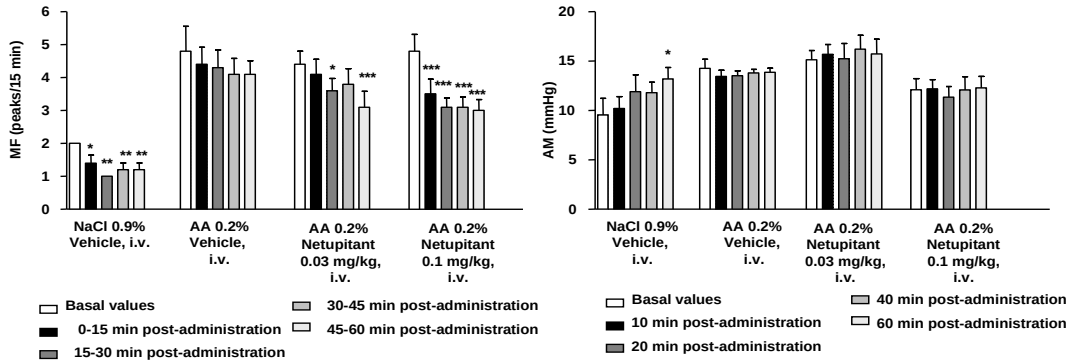
Study design, materials and methods

Female guinea-pigs were anesthetized with urethane, the jugular vein and urinary bladder were catheterized for drug administration and intravesical pressure recording, respectively. The urinary bladder was continuously infused with saline or 0.2% AA. After a 30 min stabilization period, netupitant (0.03 and 0.1 mg/kg, i.v.), tolterodine (0.003, 0.01, 0.03 and 0.1 mg/kg, i.v.) or their vehicle (glucose 5%) were administered in separate animals (n=5-10 per group). Micturition frequency (MF, peaks/15 min) and amplitude of micturition (AM, mmHg) were analyzed during the periods 0-15, 15-30, 30-45, 45-60 min and at 10, 20, 40 and 60 min post-administration, respectively.
For each cystometric parameter, the effects of tolterodine and netupitant were compared to basal values using one way ANOVA followed by Newman-Keul's test.

Results

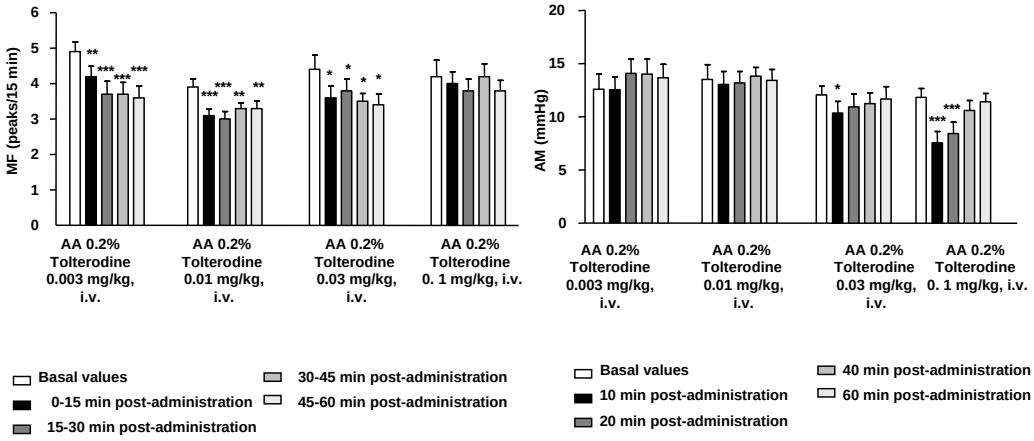
Intravesical AA (0.2%) significantly increased MF without an effect on AM (Figure 1). MF decreased significantly between 0 and 60 min in vehicle treated animals in the intravesical saline group, but not in the intravesical AA group (Figure 1). No effect on AM was observed after i.v. administration of vehicle in guinea-pigs with intravesical AA 0.2%, whereas a small increase in AM was observed at 60 min post-administration in guinea-pigs with intravesical NaCl 0.9 % (Figure 1). Netupitant at 0.03 and 0.1 mg/kg i.v. significantly decreased MF in a dose-dependent manner without significant effects on AM (Figure 1). Tolterodine significantly decreased MF at doses of 0.003, 0.01 and 0.03 mg/kg, i.v., but had no effect on MF at the highest dose (0.1 mg/kg, i.v.). In contrast, tolterodine significantly reduced AM only at the higher doses of 0.03 and 0.1 mg/kg i.v. (Figure 1).

A



*p<0.05,**p<0.01, ***p<0.001 *versus* basal values one way Anova with repeated measures followed by Newman-Keul's test (n=5-10 per group)

B



*p<0.05,**p<0.01, ***p<0.001 *versus* basal values one way Anova with repeated measures followed by Newman-Keul's test (n=5-10 per group)

Figure 1: Effect of vehicle, netupitant (A) and tolterodine (B) on micturition frequency (MF) and amplitude of micturition (AM) in anesthetized female guinea-pigs treated with intravesical AA (0.2%).

Interpretation of results

Netupitant, a selective NK_1 receptor antagonist, partially reversed the increased MF induced by intravesical AA (0.2%) in a dose-dependent manner producing a maximum change of 35 ± 4.8% at the highest dose tested (0.1 mg/kg i.v.), while having no effects on AM. Tolterodine on the other hand had an inverse dose-dependent effect on MF, producing a maximum change of 27 ± 7.1% at the lowest dose tested (0.003 mg/kg i.v.) with no effect on MF at the highest dose. In addition, correlating with the loss of effect on MF, significant inhibition of AM was observed with tolterodine at the higher doses (-34.8±8.6%).

We believe this is the first conclusive demonstration in experimental animals that low doses of tolterodine are able to decrease micturition frequency, in analogy with the effects observed in humans. In addition to mimicking the effects on micturition frequency that are observed with tolterodine in the clinic, effects on AM at higher doses suggest an inhibition of bladder smooth muscle contractility which would correlate with increases of residual volume and the urinary retention experienced by some patients.

Concluding message

Using this model we demonstrate a clear effect of tolterodine on MF at low doses and a reduction in AM at high doses, suggesting this model may be predictive of effects in the clinic. The novel NK_1 receptor antagonist netupitant was able to dose-dependently reduce micturition frequency in this model without any effects on AM, suggesting that netupitant could be efficacious in treating bladder overactivity without producing urinary retention in patients.

Specify source of funding or grant	**Helsinn SA**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**All experiment protocols were carried out in accordance with the European Community Council Directive 86/609/EEC. They were performed in accordance with french legislation concerning the protection of laboratory animals.**