

Comparison of the effects of netupitant and tolterodine on overactive bladder induced by intravesical acetic acid infusion in anesthetized female guinea-pigs

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Objectives

In multiple species, acetic acid (AA) produces bladder overactivity characterized by a decrease in intercontraction interval (ICI) (1,2).

In rats, desensitization of afferent fibers with capsaicin has been shown to prevent bladder overactivity induced by intravesical infusion of dilute AA (3). In addition, Substance P, which is present in afferent fibers appears to be a key mediator of afferent nerve function through its action (4), at NK₁ receptors.

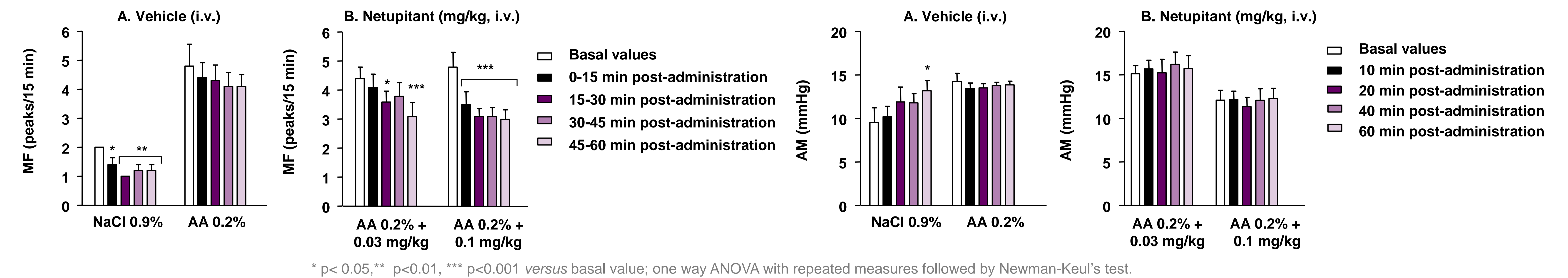
The aim of this study was to evaluate the effects of netupitant (a selective NK₁ receptor antagonist) and tolterodine (a muscarinic receptor antagonist) on cystometric parameters in AA-induced overactive bladder (OAB) in anesthetized female guinea-pigs.

Methods

- Female guinea-pigs were anesthetized with urethane (1.1 g/kg, i.p.). Catheters were inserted into the jugular vein for drug administrations and into the bladder through the dome for intravesical pressure recordings.
- The urinary bladder was continuously infused with NaCl 0.9 % or AA 0.2 % with an infusion rate of 12 ml/hr.
- After a stabilization period of 30 min, netupitant (0.03 and 0.1 mg/kg) or tolterodine (0.003, 0.01, 0.03 and 0.1 mg/kg) or their vehicle (glucose 5 %) were intravenously (i.v.) administered (1 ml in 5 min) 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, and 45-60 min and at 10, 20, 40, 60 min post-administration, respectively.
- For each parameter, the effects of vehicle, netupitant and tolterodine were compared to basal values using one way ANOVA with repeated measures followed by Newman-Keul's test.

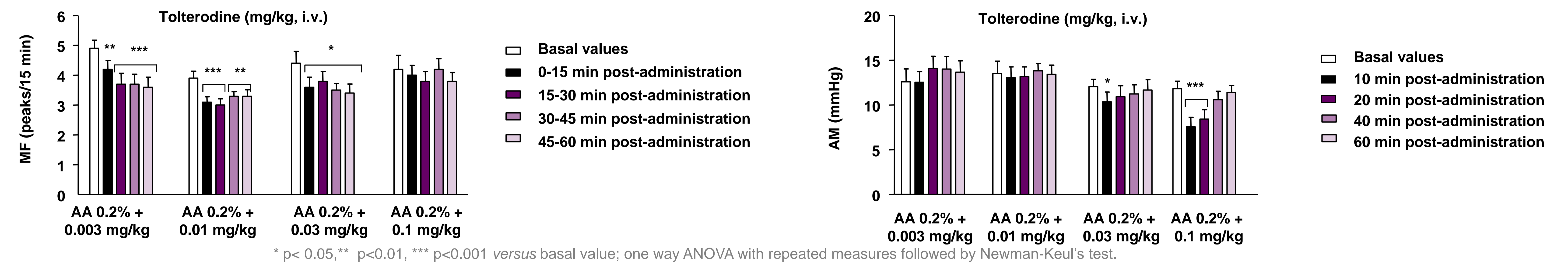
Results

Effect of vehicle (A) and netupitant (B) on MF and AM in anesthetized guinea-pigs treated with intravesical AA 0.2 %



- Intravesical AA 0.2% increased MF (4.8 ± 0.8 peaks/15 min) compared to intravesical NaCl 0.9% infusion (2.0 ± 0.0 peaks/15 min).
- Compared to basal values, netupitant, at the doses of 0.03 and 0.1 mg/kg i.v., significantly decreased MF while having no effect on AM.
- In animals with only intravesical NaCl 0.9%, there was a significant decrease in MF (0-60 min) and an increase in AM at the 60 min time point after vehicle treatment, whereas there was no change in MF or AM after vehicle treatment in animals with intravesical AA 0.2%.

Effect of tolterodine on MF and AM in anesthetized guinea-pigs treated with intravesical AA 0.2 %



- Tolterodine significantly decreased MF (0-60 min post-administration) at doses of 0.003, 0.01 and 0.03 mg/kg, i.v., but had no effect at the highest dose tested (0.1 mg/kg, i.v.).
- In contrast, tolterodine significantly decreased AM only at the higher doses of 0.03 and 0.1 mg/kg.

Conclusions

Netupitant, a selective NK₁ receptor antagonist, partially reversed the increased MF induced by intravesical AA (0.2 %) in a dose-dependent manner producing a maximum inhibition 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 inhibition 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, significant inhibition of AM was observed with tolterodine at the higher doses.

We believe this is the first 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 under antimuscarinic therapy, the effect on AM observed at higher doses suggest an inhibition of bladder smooth muscle contractility which would correlate with increases of residual volume and acute urinary retention experienced by some patients tested with tolterodine (5).

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 the effects in the clinic. The novel NK₁ receptor antagonist netupitant was able to reduce micturition frequency in dose-dependent manner in this model without any effects on AM, suggesting that netupitant could be efficacious in treating bladder overactivity without producing urinary retention in patients.

References

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