

Netupitant, a new selective NK₁ receptor antagonist, reverses acetic acid-induced bladder overactivity in anesthetized female guinea-pigs.

Philippe Lluel (1), Véronique Guilloteau (1), Marc Guerard (1), Claudio Pietra (2), Emanuela Lovati (2), Stefano Palea (1).

(1) UROsphere, Faculty of Pharmaceutical Sciences, University Paul Sabatier, Toulouse, France, (2) Helsinn Healthcare, Lugano/Pazzallo, Switzerland.

OBJECTIVES

In different species (1-2), intravesical infusion of dilute acetic acid (AA) induces bladder overactivity characterized by a large decrease in the intercontraction interval (ICI) during cystometry. In rats, it has been reported that capsaicin desensitization prevents AA-induced bladder overactivity, suggesting that AA activates capsaicin-sensitive afferent fibers (3). Several studies have suggested that the NK₁ receptor and its endogenous ligand substance P (SP) mediate urinary bladder nociceptive responses in the spinal cord (4). The aim of this study was to evaluate the effects of netupitant (Figure 1) (5) and L-733,060, a well known NK₁ receptor antagonist (6), on cystometric parameters in AA-induced bladder overactivity in anesthetized female guinea-pigs.

METHODS

Female Dunkin-Hartley guinea-pigs (body weight range 261-332 g) were anesthetized with urethane (1.5 g/kg, i.p.). A catheter was inserted into the bladder through the dome and another one into the jugular vein for drug administration. After tracheotomy, a plastic tube was inserted into the trachea. The bladder catheter was connected to a strain gauge and to a single-syringe pump. Vesical pressure was recorded continuously using a PowerLab interface and software Chart. The urinary bladder was continuously infused with saline or AA 0.2% at an infusion rate of 12 ml/hr. After the first micturition, cystometric parameters were measured for 30 minutes in order to calculate basal values, then netupitant (0.1, 0.3, 1 and 3 mg/kg), L-733,060 (3 and 10 mg/kg) or their vehicle (glucose 5%) were intravenously administered during 5 min to separate groups (n=10 per group). ICI and amplitude of micturition (AM) were analyzed at 10, 20, 40 and 60 min post-administration. For each dose the maximal effects were expressed as % of variation from basal values. ED₅₀ values (doses inducing a 50% increase in ICI) for netupitant and L-733,060 were calculated using linear regression.

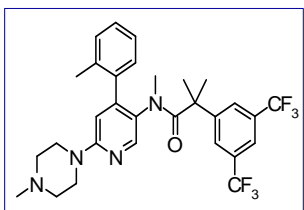


Figure 1: Chemical structure of Netupitant

In comparison to saline bladder infusion, 0.2% AA significantly ($p < 0.001$) reduced ICI (-70%; see Table 1 and Figure 2) and significantly increased AM (+164%) (Figure 2).

In 0.2% AA-treated animals, netupitant dose-dependently and significantly increased ICI from 10 to 60 min post-administration (Table 1). Maximal ICI increases were $51 \pm 15\%$, $44 \pm 8\%$, $69 \pm 8\%$ and $96 \pm 20\%$ at 0.1, 0.3, 1 and 3 mg/kg, respectively (Figure 3). The ED₅₀ value for netupitant was 0.62 mg/kg i.v..

L-733,060 also significantly increased ICI from 10 to 60 min post-administration (Table 1). Maximal effects at doses of 3 and 10 mg/kg were $40 \pm 10\%$ and $76 \pm 11\%$, respectively (Figure 3). The ED₅₀ value for L-733,060 was 5.13 mg/kg i.v..

L-733,060 at 10 mg/kg significantly decreased AM ($p < 0.05$ versus basal values). The maximal effect reached $28 \pm 5\%$, 10 min post-administration (Figure 4). Netupitant, however, did not significantly affect AM, a maximal decrease of $13 \pm 6\%$ was observed 20 min after administration of 1 mg/kg. Administration of vehicle had no effect on cystometric parameters.

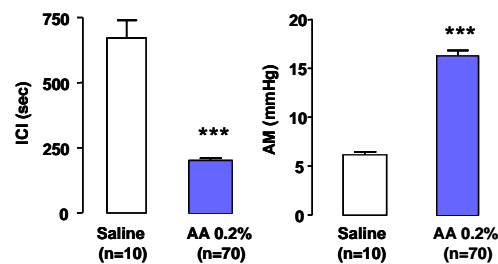
RESULTS

Table 1: Effect of vehicle, netupitant (0.1, 0.3, 1 and 3 mg/kg, i.v.) and L-733,060 (3 and 10 mg/kg, i.v.) on ICI (sec) in anesthetized female guinea-pigs with saline or AA 0.2% bladder infusion.

Bladder infusion	Intravenous treatment (mg/kg)	Basal values	Time post-administration			
			10 min	20 min	40 min	60 min
saline	Vehicle	670 ± 68	818 ± 89	829 ± 98	836 ± 91	782 ± 84 **
	Vehicle	204 ± 24 +++	208 ± 19	218 ± 18	230 ± 18	212 ± 15
AA 0.2%	Netupitant (0.1)	176 ± 21 +++	219 ± 19***	221 ± 18**	232 ± 20***	249 ± 21***
	Netupitant (0.3)	212 ± 31 +++	268 ± 35***	277 ± 33***	293 ± 37***	284 ± 35***
	Netupitant (1)	209 ± 26 +++	338 ± 31***	309 ± 32***	294 ± 43**	272 ± 31*
	Netupitant (3)	209 ± 23 +++	374 ± 27***	340 ± 23***	300 ± 29***	281 ± 32***
	L-733,060 (3)	188 ± 30 +++	254 ± 36 **	233 ± 41 *	230 ± 26 *	220 ± 23 *
	L-733,060 (10)	204 ± 16 +++	353 ± 25***	319 ± 24***	265 ± 16 **	255 ± 23 **

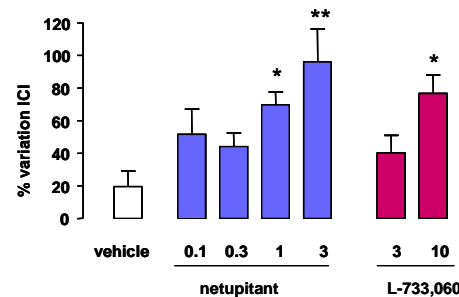
+++ $p < 0.001$ versus saline/vehicle group, one way Anova followed by Newman-Keul's test
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus basal values, one way Anova with repeated measures followed by Newman-Keul's test

Figure 2: Effect of intravesical infusion of saline or AA 0.2% on ICI and AM.



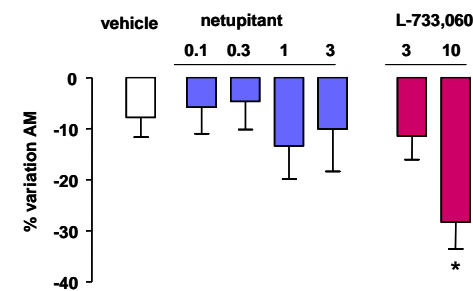
*** $p < 0.001$ versus Saline group, unpaired Student-t-test

Figure 3: Maximal effects of netupitant and L-733,060 on ICI in AA 0.2% infused bladder.



* $p < 0.05$, ** $p < 0.01$ versus vehicle group, one way Anova followed by Newman-Keul's test (n=10)

Figure 4: Maximal effects of netupitant and L-733,060 on AM in AA 0.2% infused bladder.



* $p < 0.05$ versus vehicle group, one way Anova followed by Newman-Keul's test (n=10)

CONCLUSIONS

In anesthetized female guinea-pigs, AA 0.2% induced bladder overactivity characterized by large decreases in ICI and increases in AM. Netupitant and L-733,060 dose-dependently increased ICI. Based on ED₅₀ values, netupitant was 8 fold more potent than L-733,060. Since SP is present in capsaicin-sensitive afferent fibers (7), the increase in ICI observed in this study could be explained by inhibition of bladder afferent activity by netupitant and L-733,060. Netupitant (unlike L-733,060) was without effect on bladder contractility (AM), suggesting that its use would not result in an increase of residual volume, a problem associated with the use of antimuscarinics in humans. In conclusion, this data supports the premise that netupitant could be a good candidate for the treatment of overactive bladder.

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