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COMPARATIVE ANALYSIS OF THE EFFECTS OF TOLTERODINE ON THE URODYNAMIC PARAMETERS IN NON-HUMAN PRIMATES AND RODENTS

Hypothesis / aims of study

Although antimuscarinic drugs are known to inhibit neurogenic detrusor contraction, this mechanism does not fully explain why these drugs are clinically efficacious for improving bladder storage symptoms, such as the sensation of urgency, in overactive bladder (OAB). Since it is difficult to quantify bladder sensation in animal models, bladder capacity is the most practical surrogate for bladder storage function. However, the effect of antimuscarinic drugs on bladder capacity is still controversial in rats that are the most commonly used species. Since tolterodine, an antimuscarinic drug has been reported to increase the volume which causes the first sensation of bladder filling and also to reduce the normal desire to void in healthy human subjects (1), there may be a species difference between rodents and human in the physiological role of muscarinic receptors for bladder storage function. Accordingly, we examined the effect of tolterodine on urodynamic parameters in both non-human primates and rats, and compared plasma levels of tolterodine between these species.

Study design, materials and methods

Cystometry in rhesus monkeys: Seven female rhesus monkeys with a mean weight of 5 kg were anesthetized with an intramuscular injection of Telazol (5 mg/kg) followed by intravenous constant rate infusion with ketamine (0.2 mg/kg/min). Animals were placed in a supine position and a triple lumen balloon transurethral catheter (7.4 Fr, Cook Medical) was inserted into the bladder. After confirming bladder emptiness by ultrasonography, saline was intravesically infused at 15 mL/min. After a baseline cystometry reading, tolterodine was intravenously dosed three times using a rising dose paradigm with a cystometry performed 10 min after each dose.

Cystometry in rats: Twenty seven female Sprague-Dawley rats weighing 240-260 g were anesthetized with an intraperitoneal injection of urethane (1 g/kg). Two bladder catheters (PE50) were implanted transvesically for intravesical saline infusion (0.05 mL/min) and pressure recording, respectively. Each of the urodynamic parameters was measured before and after intravenous administration of tolterodine (0.1-1 mg/kg). Data are presented as the mean ± SEM. The mean values were compared with two-way ANOVA with Bonferoni post-hoc test. A probability value less than or equal to 0.05 was considered significant.

Pharmacokinetic analysis: Plasma concentrations of tolterodine were determined by liquid chromatography-tandem mass spectrometry on an Applied Biosystems API 4000 mass spectrometer. The lower limit of quantification was 0.924 ng/mL.

Results

Tolterodine significantly increased bladder capacity with a minimum effective dose of 0.1 mg/kg in rhesus monkeys (Table 1). Micturition pressure tended to decrease and bladder compliance tended to increase with tolterodine, but neither was statistically significant at any dose. In rats, tolterodine had no effect on the bladder capacity, but decreased the micturition pressure at doses greater than 0.1 mg/kg. Pharmacokinetic analysis showed plasma levels of tolterodine overlapped in the two species (Figure 1).

Interpretation of results

The present study showed that the bladder capacity was increased after tolterodine treatment in rhesus monkeys, but not in rats at similar plasma levels. In addition, two previous studies have shown that atropine increased the bladder capacity in rhesus monkeys (2, 3). Taken together, these results suggest that the role of muscarinic receptors in bladder storage function varies between primates and rodents. In primates, muscarinic receptors may play a more active role during the storage phase to contribute to the functional bladder capacity than in rodents. However, since clinical plasma levels of tolterodine (≈ 10 nmol/L) are lower than those which increased bladder capacity in healthy rhesus monkeys, the contribution of muscarinic receptors to the OAB pathology might be different from the physiological role in normal bladder storage function.

Concluding message

A non-human primate cystometry model might be useful for examining the mechanism of action of antimuscarinic drugs or other OAB targets.

Table 1: Effect of tolterodine on urodynamic parameters in rhesus monkeys

Vehicle		Tolterodine	
Bladder Capacity, changes in mL			
(Baseline)	(171.1 ± 22.0)	(Baseline)	(161.6 ± 15.8)
Vehicle-1	4.4 ± 4.2	0.03 mg/kg	13.6 ± 13.5
Vehicle-2	10.5 ± 4.1	0.1 mg/kg	31.3 ± 9.2*
Vehicle-3	-20.6 ± 11.1	0.3 mg/kg	42.0 ± 6.4**
Micturition pressure, changes in cmH2O			
(Baseline)	(35.1 ± 2.0)	(Baseline)	(29.1 ± 2.0)
Vehicle-1	0.3 ± 3.3	0.03 mg/kg	-2.4 ± 1.1
Vehicle-2	-0.5 ± 0.7	0.1 mg/kg	-2.7 ± 1.1
Vehicle-3	2.0 ± 1.5	0.3 mg/kg	-4.5 ± 2.0
Bladder compliance, changes in mL/cmH2O			

(Baseline)	(16.3 ± 2.1)	(Baseline)	(20.7 ± 2.0)
Vehicle-1	1.1 ± 0.9	0.03 mg/kg	1.6 ± 1.4
Vehicle-2	1.9 ± 0.4	0.1 mg/kg	3.3 ± 1.2
Vehicle-3	2.3 ± 2.5	0.3 mg/kg	5.3 ± 1.2

N=5, *P<0.05, **P<0.01 vs. vehicle-control

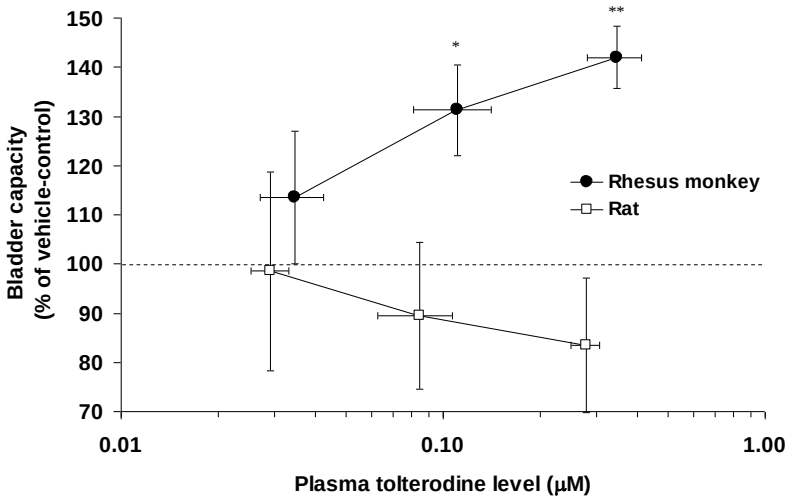

Figure 1. Plasma levels of tolterodine vs. effect on bladder capacity in rhesus monkeys (N=5) and rats (N=6-8). *P<0.05, **P<0.01 vs. vehicle-control.

References

1. Neurourol Urodyn (1995) 14; 647-655
2. J Urol (1992) 147; 185-188
3. Arzneim-Forsch/Drug Res (1997) 47; 189-194

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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	**The Institutional Animal Care and Use Committee at Merck and Co., Inc., Rahway, NJ**