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PROPIVERINE HYDROCHLORIDE INCREASES URETHRAL TONUS IN RATS

Hypothesis / aims of study

Propiverine hydrochloride (propiverine) is an anti-muscarinic agent that is used for the treatment of urinary frequency and overactive bladder. Some reports have indicated that propiverine is not only an effective treatment for urge incontinence but is also useful for stress incontinence. It has been reported that administration of propiverine for 2 weeks increases the plasma noradrenaline level by 123% and the dopamine level by 176% without changing the heart rate or blood pressure in female rats [1]. Noradrenaline in the sympathetic nerves mediates excitatory inputs to the bladder neck and the proximal urethra via α_1-adrenergic receptors, as well as inhibitory inputs to the body of the bladder via β_2- or β_3-adrenergic receptors. Therefore, the increase of circulating catecholamines after propiverine administration may activate smooth muscle in the bladder neck and the proximal urethra. Accordingly, we investigated the influence of propiverine on the bladder and urethral activity of rats.

Study design, materials and methods

Fifty-four female Sprague-Dawley rats were divided into three groups, which were a control group (n=18), a propiverine group (n=30), and an imidafenacin (anti-muscarinic agent) group (n=6). Rats in the respective groups were administered 1 ml of distilled water alone (once a day), 0.5 mg/1 ml of propiverine dissolved in distilled water (once a day), or 0.01 mg/1 ml of imidafenacin dissolved in distilled water (twice a day) by gavage using a fine catheter. After 2 weeks, a lower abdominal incision was made in the rats (6 per group) and the bladder neck was ligated under urethane anesthesia. Then bladder and urethral activity were monitored via the cystostomy and urethral catheters. In the propiverine group, the changes of bladder and urethral activity before and after intravenous injection of α1-adrenergic antagonists, such as 0.1-100 mg of prazosin (a non-selective α1-adrenergic receptor antagonist), 0.001-10 mg of silodosin (an α1A-adrenergic receptor antagonist), or 0.001-1 mg of naftopidil (an α1D-adrenergic receptor antagonist), were also recorded (n=6 each). In the control group (n=6) and the propiverine group (n=6), the leak point pressure (LPP) during electrical stimulation of the abdominal wall muscles under urethane anesthesia was recorded via the cystostomy catheter in rats that had undergone vaginal distension 4 days previously.

Results

Intravesical baseline pressure was significantly lower in the propiverine group (8.9 ± 1.4 cmH_2O, 34% decrease, P=0.007) and the imidafenacin group (10.7 ± 1.8 cm H_2O, 20% decrease, P=0.048) than the control group (13.5 ± 2.2 cmH_2O), but there was no significant difference of intravesical baseline pressure between propiverine and imidafenacin groups. The urethral baseline pressure was significantly higher in the propiverine group (22.8 ± 1.8 cmH_2O) than the control group (17.8 ± 2.3 cmH_2O, 28% increase, P=0.007) and the imidafenacin group (18.5 ± 3.5 cm H_2O, 23% increase, P=0.020). Intravenous injection of prazosin significantly decreased the urethral baseline pressure in both the propiverine group and the control group, but the percent reduction of urethral baseline pressure was greater in the propiverine group than the control group (control group: 16.0 ± 2.9 cmH_2O, a 10% decrease at 100 mg of prazosin, P=0.044; propiverine group: 18.0 ± 2.8 cmH_2O, a 21% decrease at 100 mg of prazosin, P=0.022). Intravenous injection of silodosin and naftopidil also significantly decreased the urethral baseline pressure compared with before injection in the propiverine group (silodosin: 12.6 ± 0.9 cm H_2O, a 35% decrease at 10 mg of silodosin, P=0.004, naftopidil: 15.3 ± 4.2 cm H_2O, a 25% decrease at 1 mg of naftopidil, P=0.005). In the propiverine group, the LPP was significantly higher than in the control group (34.1 ± 9.0 cmH_2O vs 20.3 ± 4.2 cmH_2O).

Interpretation of results

Anti-muscarinic agents decrease bladder compliance by blocking the binding of acetylcholine to peripheral muscarinic receptors on bladder smooth muscle. The intravesical baseline pressure was lower in the propiverine and imidafenacin groups than in the control group, but there was no significant difference of intravesical baseline pressure between the propiverine and imidafenacin groups. Therefore, the decrease of the intravesical baseline pressure may have been due to the anti-muscarinic activity of propiverine and imidafenacin. Noradrenaline is the neurotransmitter involved in excitatory sympathetic inputs to the bladder neck and the proximal urethra via α_1-adrenergic receptors. In the present study, the urethral baseline pressure was increased in the propiverine group and was reduced by administration of silodosin and naftopidil, suggesting that propiverine might stimulate smooth muscle in the bladder neck and proximal urethra via both α1A- and α1D-adrenergic receptors. Therefore, treatment using propiverine combined with an α1-adrenergic receptor antagonist may be both safe and effective for storage symptoms in men with symptomatic benign prostatic hyperplasia. The LPP of the propiverine group was significantly higher than that of the control group, indicating that propiverine increased urethral tonus. In the vaginal distension rat, intravenous injection of noradrenaline re-uptake inhibitor increases the LPP, and this increased LPP decrease by intrathecal injection of α_1-adrenergic receptor antagonists [2].The active urethral closure mechanism during stress condition is mediated by activation of somatic nerves innervating urethral and pelvic floor striated muscles. Therefore, one of the reasons of the efficacy of propiverine to stress urinary incontinence may be due to the activation of the spinal motoneurons innervating the urethral and pelvic floor striated muscles by the increased catecholamine.

Concluding message

The increase of catecholamines due to propiverine administration might stimulate the smooth muscle of the bladder neck and proximal urethra via both α1A- and α1D-adrenergic receptors, and the urethral and pelvic floor striated muscle by activation of the spinal motoneurons. This excitatory effect of propiverine on urethral may help the therapy of stress incontinence to some extent.

References

1. Biomed Res 2009; 30: 107-112.
2. Am J Physiol Renal Physiol 2007; 292: 639-646.

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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