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THE EXCITATORY EFFECT OF PROPIVERINE HYDROCHLORIDE ON THE URETHRAL ACTIVITIES IN RATS

Hypothesis / aims of study

Propiverine hydrochloride (propiverine) is used for the treatment of urinary frequency and urinary urge incontinence. For efficacy, propiverine improving urinary frequency and urge incontinence should increase bladder capacity, thus reducing voiding frequency. In various clinical trials, the efficacy and the tolerability of propiverine has been widely documented for indications ranging from detrusor hyperreflexia, detrusor hypersensitivity and hyperactivity and the enuretic syndrome. These trials focused on groups of patients with urge incontinence or urinary urgency. However, some reports show that propiverine is a safe and effective drug of choice for the treatment of patients with not only urge incontinence but also stress incontinence. Our recent report revealed that propiverine increased plasma noradrenaline and dopamine levels without change of heart rate and blood pressure in rats [1]. Noradrenaline from the sympathetic pathways provide excitatory inputs to the bladder neck and the proximal urethra via α_1-adrenergic receptors [2], as well as inhibitory input to the body of the bladder via β_2- or β_3-adrenergic receptors [3]. Therefore, high catecholamine level after oral administration of propiverine may affect to the bladder and urethral activity. On this hypothesis, we investigated the effects of propiverine in the bladder and urethral activity of rats.

Study design, materials and methods

Twelve female Sprague-Dawley rats weighing 205-240 g were used in this study. The rats were divided into two group, which were a control group (n=6), and a propiverine group (n=6). Rats from the propiverine group were administered 1 ml of propiverine dissolved in distilled water (5 mg/ml) by gavage once a day without anesthesia. Rats from the control group were administered 1 ml of distilled water by the same procedure. After 2 weeks of administration, rats were anesthetized with urethane (1.2 g/kg). A lower abdominal incision was made and both ureters were transected, after which the distal ends were ligated. The bladder neck was also ligated to produce an isovolumetric state. A polyethylene catheter (PE-50) was inserted through the dome of the bladder for cystometry, and another polyethylene catheter (PE-50) was inserted into the urethra through the external urethral meatus for measurement of the urethral pressure. A cannula was inserted into the left femoral vein for intravenous drug injection.

Bladder and urethral activity were monitored via the bladder and urethral catheters connected to a pressure transducer. The bladder was filled with physiological saline (0.05 ml/min) to above the threshold volume in order to induce isovolumetric rhythmic contractions. Physiological saline was also infused slowly (0.01 ml/min) and continuously into the urethral catheter to measure the urethral pressure. Cystometry was continued for at least 60 min, and the interval between bladder contractions, the maximal contraction pressure of the bladder, the intravesical baseline pressure, and the urethral baseline pressure were measured. After that, non-selective α_1-adrenergic antagonist (prazosin, 100 μg) were injected intravenously in each group, and the changes of bladder and urethral activity were recorded. The results were compared between the control group and propiverine group. Results are reported as the mean ± standard deviation. Student's t-test was used for statistical analysis and $p<0.05$ was considered to indicate statistical significance.

Results

There were no significant differences of the interval between bladder contractions and the maximal contraction pressure between 2 groups. However, the intravesical baseline pressure was lower (34% decrease, P=0.007) and the urethral baseline pressure were higher (41% increase, P=0.016) in the propiverine group compared with the control group. After intravenous injection of prazosin, the urethral baseline pressures were decreased in both groups, while the ratio of reduction of urethral baseline pressure in propiverine group was higher than that of control group.

Interpretation of results

In the present study, the intravesical baseline pressure was significantly lower in the propiverine group compared with the control group. Propiverine increased plasma catecholamine levels in rats [1]. Noradrenaline from the sympathetic pathways provide inhibitory input to the detrusor smooth muscle of the bladder via β_2- or β_3-adrenergic receptors [3]. Therefore, this result may be due to not only the antimuscarinic action or calcium antagonistic actions, but also the β-adrenergic action of catecholamine induced by propiverine to the detrusor smooth muscle of bladder. The urethral baseline pressure was significantly higher in the propiverine group compared with the control group. Noradrenaline from the sympathetic pathways provide excitatory inputs to the smooth muscle of the bladder neck and the proximal urethra via α_1-adrenergic receptors [2]. Therefore, this result may be due to the α_1-adrenergic action of catecholamine induced by propiverine to the smooth muscle of the bladder neck and the proximal urethra.

After intravenous injection of non-selective α_1-adrenergic antagonist, the ratio of reduction of urethral baseline pressure in propiverine group was higher than that in control group, suggesting that α_1-adrenergic antagonist may block the α_1-adrenergic action of catecholamine induced by propiverine to the smooth muscle of the bladder neck and the proximal urethra.

Concluding message

On the basis of these findings, one of the reasons of the efficacy of propiverine to stress urinary incontinence may be due to the increment of plasma catecholamine levels, and secondary inhibitory action to the detrusor smooth muscle of the bladder and excitatory action to the smooth muscle of the bladder neck and the proximal urethra.

References

1. Biomed Res 2009; 30: 107.
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Specify source of funding or grant	**None**
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	**Institutional Animal Care and Use Committee of the University of the Ryukyus**