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INFLUENCE OF PROPIVERINE, AN ANTICHOLINERGIC AGENT, ON URETHRAL ANTI-INCONTINENCE MECHANISMS IN A RAT MODEL OF STRESS URINARY INCONTINENCE: COULD THIS BE A NEW THERAPEUTIC OPTION FOR MIXED URINARY INCONTINENCE?

Hypothesis / aims of study

Anticholinergic agents are used for the treatment of OAB, and their efficacy, tolerability, and safety have been established. Recently, some anticholinergic agents such as propiverine hydrochloride have also act on other autonomic nervous systems and increase the plasma catecholamine level without an increase in blood pressure [1]. Previous studies reported that the active urethral closure mechanism prevents stress urinary incontinence (SUI) during the sneeze reflex and that the sneeze-induced continence reflex is mediated by somatic nerve-induced reflex contractions of external urethral sphincter and pelvic floor striated muscles and this mechanism is enhanced by activation of the noradrenergic system in rats [2]. Therefore, we examined the influence of propiverine hydrochloride on urethral anti-incontinence function using rats.

Study design, materials and methods

Female Sprague-Dawley rats were used in this study. The rats were divided into two groups; propiverine and vehicle groups. The propiverine group of rats were given intragastric propiverine hydrochloride (5mg) dissolved in distilled water via a catheter once a day without anesthesia. The vehicle group were administered distilled water with the same procedure. After 2 weeks of treatment, urethral function and leak point pressure (LPP) were tested under urethane anesthesia.

(1) Urethral responses were measured using a microtip transducer catheter inserted to the middle urethra from the urethral orifice. The amplitude of urethral responses during sneezing (A-URS) and urethral baseline pressure (UBP) was evaluated. Sneeze reflex was induced by a rats whisker cut and inserted into the nostril.

(2) LPP were measured using the modified vertical tilt/intravesical pressure clamp model [3]. All rats underwent spinal cord transection at the T9 level to eliminate spontaneous bladder activity. This manipulation does not interfere with the spinal continence reflexes of the bladder neck and urethra. A catheter (PE-90) was inserted into the bladder from the bladder dome and intravesical pressure was increased until fluid leakage from the urethral orifice is observed.

(3) After the experiments, blood was drawn to measure plasma concentration of catecholamines (norepinephrine, epinephrine and dopamine) using HPLC methods.

Results

No significant changes were observed in body weight between propiverine and vehicle groups after 2 weeks of treatment. (1) UBP was significantly increased in the propiverine group compared to the vehicle group (33.2 ± 1.8 vs. 26.7 ± 1.7 cmH_2O). However, significant difference was not observed in A-URS between two groups (fig.1). (2) LPP in the propiverine group was significantly higher (51.6 ± 3.0 cmH_2O) compared to the vehicle group (44.5 ± 1.6 cmH_2O). (3) Plasma norepinephrine and epinephrine levels in the propiverine group were significantly higher than those in the vehicle group (fig.2).

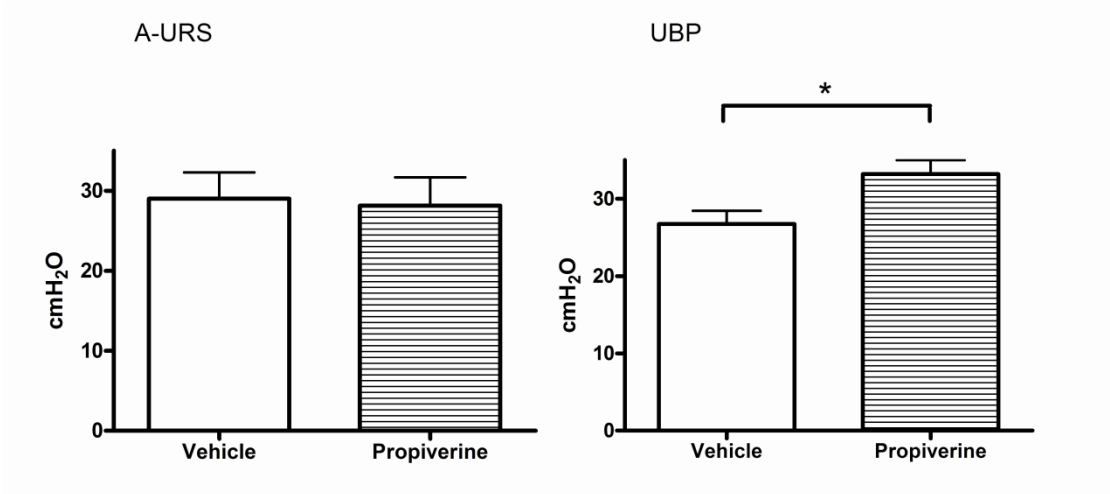

Fig.1 Amplitude of urethral pressure responses during sneezing (A-URS) and urethral baseline pressure (UBP) in vehicle and propiverine treated rats. Values are mean ± SE of data from 10 to 11 rats. *: $p<0.05$.

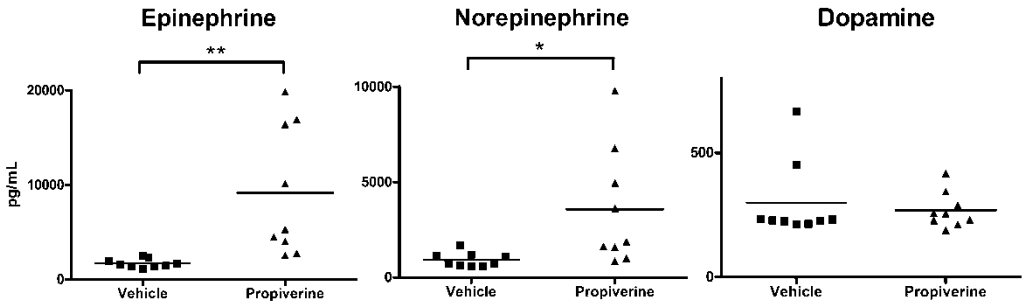

Fig.2 Effect of propiverine on plasma catecholamines. *: p<0.05, **: p<0.01.

Interpretation of results

In the present study, we investigated the chronic effect of propiverine on the urethral closure mechanism during sneeze reflex and abdominal pressure increases. In our preliminary experiments, we did not detect any changes of urethral pressure parameters tested after acute intravenous administration of propiverine (data not shown). However, following the chronic propiverine treatment (2 weeks), UBP was significantly increased along with a higher LPP during passive intravesical pressure elevation compared to vehicle treatment. It has been shown that UBP increases are mainly due to activation of sympathetic nerves in the hypogastric nerves, which induces α_1-adrenoceptor-mediated contraction of urethral smooth muscles [2] and that urethral continence reflexes induced by intravesical pressure elevation, but not those induced by sneeze, involve the activation of hypogastric nerves [3]. Thus, our results suggest that high plasma concentrations of norepinephrine and epinephrine might enhance α_1-adrenoceptor-mediated urethral smooth muscle contractions to increase UBP as well as LPP during passive intravesical pressure elevation.

Concluding message

There are some clinical studies suggesting that propiverine might improve urinary frequency as well as SUI. Our current study supports the hypothesis that high plasma catecholamine concentrations after the chronic propiverine treatment could contribute to the improvement of SUI conditions. Therefore, propiverine could be a good therapeutic candidate for mixed urinary incontinence.

References

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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**
Name of ethics committee	**University of Pittsburgh Institutional Animal Care and Use Committee**