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COMPARISON OF EFFECTS OF VARIOUS ANTIMUSCARINIC DRUGS ON CYSTOMETRIC FINDINGS IN CHRONIC SPINAL RATS

Hypothesis / aims of study

Antimuscarinic drugs are using for treatment of urinary incontinence and frequency in patients with spinal cord injury. The efficacy and safety of antimuscarinic drugs is clinically established. However, the comparison of the effects of various antimuscarinic drugs on cystometric findings in spinal cord injury are not been fully evaluated. In the present study, we examined the effects of several antimuscarinic drugs on cystometric findings in chronic spinal rats.

Study design, materials and methods

Spinal cord was transected at the level of Th 8-9 in female Sprague-Dawley rats. Sham-operated rats were used for the control. The experiments were performed 10 weeks after surgery. In each rats, urinary volume and micturition frequency were measured for 3 days. Then, the rats were implanted with femoral vein and bladder dome tubing for filling cystometry under anesthesia. Cystometrograms were performed using constant infusion (0.05 ml/min) of saline into the bladder to elicit voiding. Saline voided from the urethral meatus was collected and measured to determine the voided volume. After several cystometrograms were performed in the same animal, the infusion was stopped at the beginning of a voided contraction. The residual volume was then measured by aspiration of the residual saline through the intravesical catheter. After stable voiding cycles were established, each rat received a single intravenous administration of test drug at a volume of 1 ml/kg. The cystometric parameters measured were the micturition volume and frequency, residual urine, micturition pressure, micturition threshold pressure, number and pressure of non-voided contraction. The effects of tolterodine (0.01-0.1 mg/kg), solifenasin (0.01-0.3mg/kg) and propiverine (0.03-1 mg/kg) on the parameters were compared.

Results

In spinal rats, micturition frequency, micturition pressure, micturition threshold pressure and the number and amplitude of non-voided contractions were significantly higher, as compared to the normal rats. Micturition volume and residual urine in spinal rats was significantly decreased and increased, respectively. All three antimuscarinic drugs significantly improved micturition volume, frequency, and residual urine, in the concentration dependent manner. Propiverine and solifenacin did not have significant effects on micturition threshold pressure. However, the highest dose of tolterodine (0.1 mg/kg) significantly increased micturition threshold pressure and decreased the micturition pressure (Table). All drugs decreased the number of non-voided contraction. The inhibition rate of the non-voided contraction by propiverine (52.3%; 1 mg/kg) was significantly higher, as compares with tolterodine (20.3%; 0.1 mg/kg) and solifenacin (35.1%; 0.3mg/kg).

Interpretation of results

In the present experiment, the effects of tolterodine, solifenasin and propiverine were different. The difference may be due to the difference in the pharmacological characteristic of each drug. Tolterodine is pure antimuscarinic drug without selectivity for muscarinic receptor subtypes. Solifenasin is also pure antimuscarinic drug with a relative selectivity for M_3 receptor subtype. Propiverine dose not have significant muscarinic receptor subtype selectivity. It has both antimuscarinic and Ca^{2+} channel inhibitory actions. Although the mechanism for non-voided contraction in chronic spinal rat dose not clearly elucidated, the present data suggest that Ca^{2+} channel inhibitory action of propiverine may be related to the inhibitory effect of the contraction.

Concluding message

The present results demonstrate that efficacies of various antimuscarinic drugs on cystometric findings are different. The difference may be related to the different pharmacological characteristics of the drugs. The Ca^{2+} channel inhibitory action of propiverine may contribute to the favorable result of the inhibition in non-voided contraction.

Table. Effects of various antimuscarinic drugs on parameters of cytometrogram

Drug	Dose (mg/kg)	Number of non-voided contraction	Micturition volume (ml)	Residual volume (ml)	Micturition pressure (cmH_2O)	Threshold pressure (cmH_2O)
Tolterodine	Pre	12.3±2.9	0.61±0.07	0.75±0.12	60.2±8.7	15.4±3.7
(n=8)	0.01	12.4±2.4	0.68±0.13	0.77±0.10	58.5±9.5	18.4±5.5
	0.03	11.3±1.9	0.75±0.11	0.65±0.14	55.6±6.8	22.4±4.8
	0.1	9.8±1.7*	0.83±0.10*	0.60±0.10*	40.2±5.9*	26.4±4.7*
Solifenacin	Pre	13.1±2.5	0.65±0.11	0.77±0.15	62.2±10.2	14.4±3.7
(n=6)	0.01	12.4±2.0	0.72±0.12	0.75±0.12	60.4±6.7	14.8±2.5
	0.03	11.3±1.9	0.80±0.10	0.65±0.11	58.2±8.7	15.4±2.1
	0.1	10.5±1.7	0.85±0.14*	0.60±0.13	54.2±7.1	15.9±4.1

	0.3	8.5±1.9*	0.90±0.13*	0.58±0.12*	48.2±6.7*	16.4±3.0
Propiverine	Pre	13.4±2.3	0.62±0.12	0.78±0.10	60.8±8.7	15.4±2.5
(n=10)	0.03	11.3±2.9	0.64±0.10	0.76±0.10	59.8±9.7	15.1±3.2
	0.1	10.0±1.9	0.72±0.12	0.70±0.12	61.2±8.2	15.4±2.7
	0.3	8.5±2.2*	0.88±0.10*	0.58±0.12*	58.2±10.4	16.0±4.2
	1	6.3±1.5*	0.92±0.12*	0.55±0.11*	55.2±8.7	16.5±3.7

* P< 0.05 as compared with the data of pre-treatment in each drug

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