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INTRAVESICAL INSTILLATION OF HUMAN URINE AFTER ORAL ADMINISTRATION OF TROSPIUM, TOLTERODINE AND OXYBUTYNIN IN A RAT MODEL OF DETRUSOR OVERACTIVITY

Hypothesis / aims of study
This study is designed using a rat model of detrusor overactivity and human urine for intravesical instillation after ingestion of antimuscarinics to determine if there is a local bladder effect

Study design, materials and methods
This study was designed in two phases. The direct instillation phase was designed to continuously infuse 0.1 and 0.5 □g/ml of oxybutynin, trospium, tolterodine, and dimethindene (M_2-selective muscarinic receptor antagonist) into the rat bladder. The doses chosen were based on calculated urine-excreted concentrations of trospium typically achieved from human oral treatment of 40 mg/day. The effect of carbachol with and without the low-dose agents was then assessed.

The second phase involved urine collection from two healthy adult volunteers after each volunteer ingested five days of trospium (20 mg bid), tolterodine LA (4 mg qd) and oxybutynin XL (10 mg qd). The drugs were taken in a random order with seven days washout period between each drug. After the fifth day of drug, the urine collected from two volunteers were mixed together and then blindly labeled and used for rats testing. Control human urine (without oral antimuscarinics)was also included. Under urethane anesthesia (1.2gm./kg.), the effect of intravesical administration of human urine on carbachol-induced bladder overactivity was studied in female S-D rats. Cystometric parameters were measure during continuous infusion (0.04ml/min) for over one hour each of saline, human urine, then mixture of carbachol (30 □M) and human urine were compared in four groups (control and 3 different antimuscarinics tested; n=6 in each group).

Results

In the direct drug instillation protocol, none of the cystometric parameters were altered with antimuscarinic agents alone. Intercontraction interval (ICI) was decreased with intravesical carbachol (65 □ 0.1% compared with baseline), but this was prevented with concomitant antimuscarinics. Human urines with or without intake of antimuscarinic agents had no effect on normal bladder function.

Table. Cystometric parameters of intravesical instillation of saline and human urine without and with carbachol.

	Drugs taken	No.	Saline	Urine	Urine with carbachol
Intercontraction interval (sec.)	Control	6	764±113	756±123	346±96
	Oxybutynin	6	738±73	778±64	431±84
	Tolterodine	6	819±99	838±106	341±66
	Trospium	6	874±116	849±143	894±176
Bladder capacity (mL)	Control	6	0.48±0.06	0.46±0.06	0.21±0.07
	Oxybutynin	6	0.46±0.05	0.50±0.04	0.25±0.06
	Tolterodine	6	0.53±0.08	0.51±0.08	0.20±0.04
	Trospium	6	0.60±0.10	0.60±0.11	0.62±0.12
Maximum voiding pressure (cmH2O)	Control	6	37.2±1.8	36.7±2.5	42.0±2.7

	Oxybutynin	6	33.6±2.2	32.2±1.7	34.9±2.7
	Tolterodine	6	33.2±1.4	32.6±1.1	34.5±2.4
	Trospium	6	29.8±16	28.8±1.8	30.3±3.3

Interpretation of results

Because dimethindene did not affect bladder capacity and ICI in normal voiding but was able to suppress carbahol-induced detrusor overactivity, M2 receptors may not be involved in afferent pathways during normal voiding but could be involved in these pathways in a situation with high acetylcholine release, such as in the case of detrusor overactivity.

Bladder capacity and intercontraction intervals were significantly decreased after an addition of carbachol to human urine containing vehicle, tolterodine or oxybutynin. Human urine after ingestion of trospium, however, prevented the carbachol-induced reduction in bladder capacity and intercontraction intervals. Maximum voiding pressure and pressure threshold were not changed in any case.

Concluding message

The results of this study suggest that antimuscarinic agents have a local bladder topical effect during the bladder storage phase in addition to the smooth muscle mediated voiding phase. Antimuscarinic agents may be effective in treating overactive bladder, not only by suppression of muscarinic receptor-mediated detrusor muscle contraction, but also by blocking muscarinic receptors in bladder-afferent pathways. Drugs, such as trospium, that are excreted into the urine in metabolically active form may have this unique effect.

FUNDING: **Indevus**