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Title: COMPARISON OF PHARMACOLOGICAL EFFECTS OF VARIOUS ANTIMUSCARINIC DRUGS ON HUMAN ISOLATED URINARY BLADDER

Aims of study

Several antimuscarinic drugs are clinically used, and clinical trials of newly synthesized antimuscarinic drugs for the treatment of overactive bladder are now going. Pharmacological studies have demonstrated the affinity and selectivity for muscarinic receptor subtype and selectivity for the bladder of the drugs. However, there is little information available on the comparison of the effects of these drugs on human detrusor smooth muscles. Therefore, the present study was performed to compare the effects of various antimuscarinic drugs (atropine, oxybutynin, propiverine, temiverine, vamicamide, tolterodine, KRP-197, darifenacin) on human isolated urinary bladder. Furthermore, using microdialysis method, prejunctional effects of these drugs on electrical field stimulation (EFS)-induced acetylcholine (ACh) release were also evaluated.

Methods

Human urinary bladders (54 male and 5 female: mean age 66.4 years) were obtained from patients undergoing radical cystectomy due to bladder carcinoma. Smooth muscle strips were dissected from the body of urinary bladder of each patient. Each strip, which was suspended in an organ bath filled with oxygenated Krebs-Henseleit solution, was connected to an isometric force displacement transducer, and an isometric tension development was recorded. The effects of pretreatment with various drugs on the contractile responses induced by carbachol (CCh), KCl, $CaCl_2$ and EFS (supramaximum voltage, 0.3 msec duration, 2-60 Hz and 3 sec train) were evaluated. Furthermore, in ACh release experiments, the microdialysis probe was inserted into the strip, and Ringer solution was perfused into the probe. The dialysate during EFS (supramaximum voltage, 0.5 ms pulse duration, 60 Hz and 3 s train at 1 min interval for 10 min) was collected, and the amount of ACh released in the dialysate was measured by HPLC with ECD. The effects of pretreatment with various antimuscarinic drugs on ACh release in human bladder were evaluated.

Results

CCh (10^{-8}-10^{-3} M) induced concentration-dependent contractions of human detrusor smooth muscles. Pretreatment with various antimuscarinic drugs caused typical shifts to the right of the concentration-response curves for CCh, except for higher concentrations (10^{-5} M) of oxybutynin, propiverine and temiverine, which caused decreases of about 20 – 40 % of the maximum contractile responses to CCh. All slopes of the regression lines of Schild plots were close to unity, and the rank order of pA_2 values was: darifenacin ≥ KRP-197 ≥ atropine = tolterodine ≥ oxybutynin ≥ vamicamide > propiverine = temiverine (table). Darifenacin, KRP-197, vamicamide, tolterodine and atropine did not inhibit the KCl (80 mM) and $CaCl_2$ (5 mM)-induced contractions, while oxybutynin, propiverine and temiverine (10^{-7}-10^{-5} M) significantly inhibited the contractions. EFS caused frequency-dependent contractions of human detrusor smooth muscles, which were significantly inhibited by various drugs. In the presence of 10^{-6} M atropine, darifenacin, KRP-197, vamicamide and tolterodine did not inhibit the residual contractions induced by EFS at any frequencies, while oxybutynin, propiverine and temiverine (10^{-5} M), significantly inhibited the atropine-resistant part of the contractions. EFS caused significant increase in ACh

elease from cholinergic nerve endings in human detrusor smooth muscles. Pretreatment with KRP-197 and oxybutynin caused significant enhancements of EFS-induced ACh release. However, other drugs did not have significant effect on EFS-induced ACh release.

Table: Comparison of pA_2 values of Schild plots of various antimuscarinic drugs in human detrusor smooth muscles

Antimuscarinic drug	pA2	Slope
Atropine (n=8)	9.06±0.09	0.92±0.04
Oxybutynin (n=8)	8.63±0.11	0.97±0.04
Propiverine (n=8)	7.94±0.06	1.01±0.05
Temiverine (n=10)	7.95±0.06	1.03±0.06
Vamicamide (n=8)	8.44±0.04	1.05±0.02
Tolterodine (n=10)	9.04±0.10	0.97±0.04
KRP-197 (n=10)	9.12±0.10	1.13±0.09
Darifenacin (n=10)	9.54±0.36	1.01±0.13

Conclusions

The present results demonstrate that pharmacological effects of various drugs on human detrusor smooth muscles are different. And, some drugs may have prejunctional inhibiting actions of ACh release from cholinergic nerve endings. The present data are useful information for clinical use of these drugs in treatment of overactive bladder.

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