CONCLUSION: Our data indicate that urinary retention and especially subsequent catheterization cause bladder injury. This bladder injury is, in some part, caused by ischemia-reperfusion, and lipid peroxidation may play an important role in the bladder dysfunction.

TABLE

	Emax (g/mm²)	MDA (μM/g tissue)	4-HNE (μM/g tissue)
A	11.8 ± 1.3	1.27 ± 0.11	1.19 ± 1.02
B	11.9 ± 1.7	1.24 ± 0.06	1.30 ± 0.98
C	9.8 ± 1.3	1.08 ± 0.08	1.33 ± 0.77
D	6.9 ± 0.7*	1.75 ± 0.24*	8.31 ± 2.09*

*) significantly different from group A, B and C. $P < 0.05$ is level of significance.

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PHARMACOLOGICAL EFFECTS OF A NEW MUSCARINIC RECEPTORS ANTAGONIST: KRP-197 ON HUMAN ISOLATED URINARY BLADDER

Aims of Study

KRP-197 (4-(2 methlimidazolyl)-2,2-diphenylbutyramide) is a newly synthesized antimuscarinic drug, and clinical trials for the treatment of pollakisuria and urinary incontinence are now going. The pharmacological studies have demonstrated that this compound has a potent affinity and selectivity for M3 muscarinic receptor subtypes and no calcium antagonistic actions. Furthermore, this drugs exhibited a favorable selectivity for the bladder as compared with the salivary glands. However, there is little information available on the effects of KRP-197 on human detrusor smooth muscles. Therefore, the present study was undertaken to determine the effects of KRP-197 on the human isolated urinary bladder using muscle bath technique. Furthermore, the pharmacological action of KRP-197 was compared with that of other antimuscarinic drugs (atropine, oxybutynine and propiverine).

Methods

In this study, human urinary bladders were obtained from 20 patients (18 male and 2 female: mean age 67.8 years) 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 thermostatically controlled organ bath filled with oxygenated Krebs-Henseleit solution, was connected to an isometric force displacement transducer, and an isometric tension development was recorded. And the pretreatment with KRP-197, atropine, oxybutynine and propiverine on the contractile responses induced by carbachol (CCh), KCl, $CaCl_2$ and electrical field stimulation (EFS; supramaximum voltage, 0.3 msec duration, 2-60 Hz and 3 sec train) were evaluated.

Results

CCh (10^{-9}-10^{-2} M) induced concentration-dependent contraction of human detrusor smooth muscles. Pretreatment with KRP-197 (10^{-9}-10^{-7} M), atropine (10^{-9}-10^{-6} M), oxybutynine (10^{-8}-10^{-6} M) and propiverine (10^{-8}-10^{-6} M) caused typical shifts to the right of the concentration-response curves for CCh, except for higher concentrations (10^{-5} M) of oxybutynin and propiverine, which caused a decrease of about 30 % of the maximum contractile responses to CCh. All the slopes of the regression lines of Schild plots were close to unity, and the rank order of pA_2 values was: atropine = KRP-197 ≥ oxybutynine > propiverine (table). KRP-197 (10^{-9}-10^{-7} M) and atropine (10^{-9}-10^{-6} M) did not inhibit the KCl (80 mM) and $CaCl_2$ (5 mM)-induced contractions, while oxybutynine (10^{-8}-10^{-5} M) and propiverine (10^{-8}-10^{-5} M) significantly inhibited the contractions. EFS caused frequency-dependent contraction of human detrusor smooth muscles, which were significantly inhibited by various drugs. In the presence of 10^{-6} M atropine, KRP-197 did not inhibit the residual contractions induced by EFS at any of the frequencies, while oxybutynin (10^{-5} M) and propiverine (10^{-5} M) significantly inhibited the atropine-resistant part of the contractions.

Table: pA_2 values and slopes of Schild plots for various drugs on human detrusor smooth muscles

Drugs	n	pA_2	Slope
KRP-197	8	9.12±0.10	1.13±0.09
Atropine	8	9.06±0.09	0.93±0.04
Oxybutynin	8	8.63±0.11	0.97±0.04
Propiverine	8	7.94±0.06	1.01±0.05

Conclusions

The present results suggest that the inhibitory effects of KRP-197 is mediated only by the antimuscarinic action, which is equal to that of atropine and oxybutynin, and significantly greater than that of propiverine, and that KRP-197 has neither Ca^{2+} channel antagonistic action nor inhibitory effect on the atropine-resistant part of the contractions in human detrusor smooth muscles. These findings support the usefulness of KRP-197 as a therapeutic drug for overactive bladder with symptoms of frequency, urgency and urge incontinence.

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IN VIVO INVESTIGATIONS OF TWO ANTICHOLINERGIC DRUGS ON BLADDER CONTRACTION AND SALIVARY FLOW