**131**

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**Title:** PHARMACOLOGICAL EFFECTS OF DARIFENACIN ON HUMAN ISOLATED URINARY BLADDER

**Aims of Study :**

Darifenacin is a new antimuscarinic drug and clinical trials for the treatment of overactive bladder with symptom of pollakisuria and urge urinary incontinence are now going. It is reported that darifenacin has high affinity for M3 receptors, and selectivity for urinary bladder smooth muscle in vitro and vivo animal experiments. However, there is little information on the effects of darifenacin on human smooth muscles of urinary bladder. Therefore, the present study was performed to evaluate the effects of darifenacin on human detrusor smooth muscles.

**Methods :**

Specimens of human urinary bladder were obtained from 20 patients who underwent total cystectomy due to malignant bladder tumor. Smooth muscle strips were dissected from the dome-part of urinary bladder. Each strip was suspended in an organ bath filled with 5%$CO_2$-95%$O_2$ gassed Krebs-Henseleit solution. We investigated the effects of darifenacin and atropine on the contractions induced by carbachol (CCh), 80 mM KCl, 5 mM CaCl2 and electrical field stimulation (EFS; supramaximum voltage, 0.3 msec duration, 2-60 Hz, 3 sec train) in the detrusor strips.

**Results:**

CCh (0.01 μM - 10 mM) caused concentration-dependent contractions.Darifenacin (0.1 nM - 0.1 μM) and atropine (0.1 nM - 0.1μM) caused parallel shifts to the right of the concentration-response curves to CCh. All slopes of the regression line of Schilld plots were close to unity, and the pA2 values of darifenacin and atropine were 9.54 and 9.57, respectively. Both darifenacin and atropine did not inhibit the maximum contractions to CCh. EFS (0.3 msec duration, 2-60 Hz and 3 sec train) caused frequency-dependent contractions, and which were inhibited by atropine and darifenacin in a concentration-dependent manner. In the presence of atropine (1μM),darifenacin did not inhibited the residual atropine resistant contractions induced by EFS.

**Conclusions :**

The present study showed that darifenacin inhibited contractions of human detrusor smooth muscles by its antimuscarinic action. This finding suggests that darifenacin would be useful for the treatment of overactive bladder with symptoms of pollakisuria and urge urinary incontinence.

**Table: pA2 values and slopes of Schild plots for darifenacin and atropine on human detrusor smooth muscles**

| Drugs | n | pA2 | slope |
|---|---|---|---|
| Darifenacin | 10 | 9.54 ±0.36 | 1.01 ±0.13 |
| Atropine | 8 | 9.57 ±0.60 | 1.19 ±0.34 |