641

Lee M J[1], Moon J[1], Lee H K[1], Choi S H[1]
1. *Dong-A ST Research Institute*

FUNCTIONAL SELECTIVITY FOR URINARY BLADDER OVER SALIVARY GLAND AFTER ORAL ADMINISTRATION OF A NOVEL MUSCARINIC RECEPTOR 3 ANTAGONIST, DA-8010 IN MICE

Hypothesis / aims of study
DA-8010 is a novel Muscarinic receptor 3 antagonist being developed for the treatment of overactive bladder and urinary incontinence. The currently available antimuscarinics are associated with a high incidence of side effects, such as dry mouth, which often leads to discontinuation of treatment. The purpose of this study was to elucidate the functional selectivity of DA-8010 for urinary bladder over salivary gland. We investigated the muscarinic receptor binding, the inhibitory effects on carbachol (CCh)-induced intravesical pressure (IVP) elevation and salivary secretion after oral administration of DA-8010 in mice.

Study design, materials and methods
DA-8010 (3 mg/kg), solifenacin (30 mg/kg) and oxybutynin (30 mg/kg) were orally administered to male ICR mice to characterize their *in vivo* muscarinic receptor binding in the bladder and submaxillary gland tissues using [N-methyl-^{3}H]-scopolamine at 0.5 to 24 hours after administration. The effects of oral DA-8010 (1 and 3 mg/kg) on CCh-induced IVP and salivation were evaluated in non-fasted, anesthetized, female mice. IVP evaluation was represented as the difference between baseline and peak pressure observed after CCh injection. The amount of salivary secretion was calculated as the difference in the weight of the cotton ball before and after insertion.

Results
In the mouse bladder, the dissociation constant (K_d) value for DA-8010 reached a maximum value at 0.5 hours and was maintained for at least 24 hours. Solifenacin exerted similar but lower K_d values compared to DA-8010, while oxybutynin did not show a significant increase in K_d value compared to vehicle control in the bladder. In the submaxillary gland, oxybutynin showed a faster and greater increase of K_d value at 0.5 hours after administration compared to DA-8010 and solifenacin. DA-8010 and solifenacin reached a maximum K_d at 2 h, and showed moderate K_d values. There was a rapid decline of K_d values for all 3 compounds, and they were not significantly different from the control value at 6 hours.
Oral DA-8010 (1 and 3 mg/kg) also inhibited CCh-induced IVP elevation and salivary secretion. DA-8010 showed significant effects on bladder for 12 h at 1 mg/kg and for 24 h at 3 mg/kg after oral administration compared to vehicle control. Otherwise, inhibition of salivation was observed at only early time (2 h after administration at 1 mg/kg and 6 h after administration at 3 mg/kg). In addition, DA-8010 was significantly more potent in inhibiting IVP elevation compared to inhibition of salivation at 12 h after administration of 1 and 3 mg/kg.

Interpretation of results
DA-8010 administered orally, compared with solifenacin and oxybutynin, showed more selective and persistent binding for muscarinc receptors in the mouse bladder than in the salivary gland. In addition, oral DA-8010 inhibited CCh-induced IVP elevation more potently than salivation in mice.

Concluding message
DA-8010, a novel muscarinic receptor 3 antagonist showed a more selective and longer-lasting effect to muscarinic receptors in the bladder than salivary gland compared to currently available drug therapies. These findings provide further evidence for the clinical use of DA-8010 as a promising drug with its greater efficacy for overactive bladder and potentially less side effects of dry mouth.

References
1. Benner JS, Nichol MB, Rovner ES et al. Patient-reported reasons for discontinuing overactive bladder medication. BJU Int 2010;105:1276-1282
2. Chapple CR, Khullar V, Gabriel Z et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urology 2008;54:543-562
3. Tomomi Oki, Shuichi Sato, Keiji Miyata, Shizuo Yamada Muscarinic receptor binding, plasma concentration and inhibition of salivation after oral administration of a novel antimuscarinic agents, solifenacin succinate in mice. Br J Pharmacol 2005;145:219-227

Disclosures
Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Mouse **Ethics Committee:** The institutional animal care and use committee of Dong-A ST research institute