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# IN VIVO BLADDER SELECTIVE PROFILE OF SOLIFENACIN SUCCINATE (YM905) OVER SALIVARY GRAND IN MICE AND RATS

## Aims of Study

Antimuscarinic agents are widely used for the treatment of overactive bladder (OAB). However, the use of these agents is often limited by severe adverse effects, particularly dry mouth. The present studies investigated the tissue selectivity of solifenacin succinate (YM905), a novel muscarinic receptor antagonist being developed for the treatment of OAB, for urinary bladder over salivary gland in mice and rats, and compared the results with those of other antimuscarinics such as tolterodine, oxybutynin and darifenacin in vivo.

## Methods

Carbachol (CCh)-induced intravesical pressure (IVP) elevation and salivary secretion were determined in pentobarbital-anesthetized mice and rats. A polyethylene catheter was inserted into the bladder via the urethra. The bladder was emptied by drainage of urine through a catheter, $\leq$ 0.1 mL (mice) or $\leq$ 1 mL (rats) of physiological saline was then infused into the bladder. IVP was measured with a pressure transducer connected to a catheter. The tail vein was cannulated with an injection needle to enable drug administrations. Thereafter, antimuscarinics were given intravenously prior to intravenous administration of cumulative or single dose of CCh. Saliva was collected with filter papers, and salivary secretion was estimated from the area of spots (mice) or from the weight of papers (rats). In rats, potency was estimated as the dose required to produce 30% inhibition ($ID_{30}$) in CCh (0.01 mg/kg i.v.)-induced IVP elevation or salivary secretion for each antimuscarinic agent. Bladder selectivity ratio (R) was calculated by the following equation: R = [$ID_{30}$ (salivary secretion)] / [$ID_{30}$ (IVP elevation)].

## Results

Solifenacin did not inhibit CCh-induced salivary secretion at doses that potently inhibited CCh-induced IVP elevation in anesthetized mice. In anesthetized rats, solifenacin inhibited CCh-induced IVP elevation ($ID_{30}$ = 0.023 mg/kg i.v.) more potently than salivary secretion ($ID_{30}$ = 0.15 mg/kg i.v.) (Table 1). The bladder selectivity ratio of solifenacin (R = 6.5) was greater than those of tolterodine (R = 2.4), oxybutynin (R = 1.1) and darifenacin (R = 1.2).

**Table 1. Inhibitory effects of solifenacin and other antimuscarinics on CCh-induced IVP elevation and salivary secretion in anesthetized rats**

| Antimuscarinics | $ID_{30}$ value (mg/kg i.v.) [95% confidence limits] | | Bladder selectivity ratio (R) |
|---|---|---|---|
| | IVP elevation | Salivary secretion | |
| Solifenacin | 0.023 [0.010 - 0.039] | 0.15 [0.11 - 0.24] | 6.5 |
| Tolterodine | 0.010 [0.008 - 0.014] | 0.024 [0.016 - 0.047] | 2.4 |
| Oxybutynin | 0.027 [0.015 - 0.045] | 0.030 [0.024 - 0.038] | 1.1 |
| Darifenacin | 0.0098 [0.0064 - 0.0150] | 0.012 [0.009 - 0.017] | 1.2 |

$ID_{30}$ values were determined by the linear regression analysis (n = 6).

**Conclusions**

These in vivo studies suggest that solifenacin has higher tissue selectivity for urinary bladder over salivary gland in mice and rats. Therefore, solifenacin may improve the symptoms of OAB potently with a low incidence of adverse effects, such as dry mouth, in humans.