

## EFFICACY OF PILOCARPINE HYDROCHLORIDE ON CONTRACTION OF THE PORCINE AND HUMAN URINARY BLADDER IN VITRO, AND IN THE TREATMENT OF VOIDING DIFFICULTY IN PATIENTS WITH DETRUSOR UNDERACTIVITY

### Hypothesis / aims of study

The treatments of voiding dysfunction caused by detrusor underactivity have been less than satisfactory, leaving new treatment drugs awaited. The aim of this study is to investigate the efficacy of pilocarpine hydrochloride, which is a M<sub>3</sub>-muscarinic receptor agonist used for the treatments of dry mouth accompanied with several disease such as Sjogren syndrome, on contraction of porcine and human urinary bladder, and furthermore, in the treatment of voiding dysfunction in patients with detrusor underactivity.

### Study design, materials and methods

Porcine and human urinary bladder were mounted in 10ml organ baths containing Krebs solution which was maintained at 37°C and continuously gassed with 95% O<sub>2</sub> and 5%CO<sub>2</sub>. The tissues were subjected to a resting tension of 1 g and allowed to equilibrate for 60 minutes. Cumulative concentration-response curves (CRCs) to pilocarpine were obtained, with Krebs solution containing in the presence of darifenacin, 4-DAMP (M<sub>3</sub> selective antagonist), pirenzepine (M<sub>1</sub> selective antagonist), methoctramine (M<sub>2</sub> selective antagonist), or in the presence of vehicle. Affinity values for each antagonist were calculated. Next, patients with detrusor underactivity were enrolled the clinical study. They had administrated one tablet of Salagen® which contains 5 mg of the test substance per tablet, as pilocarpine hydrochloride 3 times daily, after each meal, for 8 weeks. At the end point of study, the efficacy was estimated by the change in maximum urinary flow rate (Q<sub>max</sub>), IPSS (total and subtotal score), QOL score, maximum detrusor pressure at Q<sub>max</sub> (P<sub>det</sub> Q<sub>max</sub>), and average urinary flow rate (Q<sub>ave</sub>), and the safety was estimated by the change in incidence of adverse events, and so on.

### Results

In vitro, pilocarpine induced contractions of smooth muscle of the porcine detrusor in a concentration-dependent manner, with maximum contraction relative to 80 mM KCl of 134.4±22.3% and pEC<sub>50</sub> values of 5.28±0.26. Darifenacin, 4-DAMP, pirenzepine, and methoctramine caused surmountable antagonism of responses to pilocarpine, with slopes of Schild plot of no significant difference with 1. The rank order of mean pA<sub>2</sub> values was as follows: 4-DAMP (8.79±0.27) = darifenacin (8.73±0.06) > pirenzepine (6.72±0.12) > methoctramine (6.58±0.16). In the human bladder, pilocarpine induced contractions of smooth muscle of the porcine detrusor in a concentration-dependent manner. Darifenacin caused surmountable antagonism of responses to pilocarpine, with slopes of Schild plot of 0.93±0.30. As a results of the clinical study, twelve out of 17 patients (mean age was 64.3 ±17.9 years old) completed this study. IPSS total score (15.8±9.4 to 12.1±9.0 points, *p*=0.0039), voiding symptom subtotal score (9.3±6.1 to 7.3±5.7 points, *p*=0.0469), residual urine volume (222.7±122.3 to 102.4±92.9ml, *p*=0.0020), Q<sub>max</sub> (9.1±4.6 to 12.9±5.5ml/s, *p*=0.0313), Q<sub>ave</sub> (6.1±5.3 to 8.8±6.3 ml/s, *p*=0.0039), and voided volume (158.8±114.5 to 186.8±110.0 ml, *p*=0.0273) all significantly improved. Four patients discontinued because of the adverse events such as the hypersalivation, discomfort of the stomach, and 1 patient didn't come to the hospital for some unknown reason.

### Interpretation of results

By the in vitro study, it was shown that the rank order of mean pA<sub>2</sub> values was the highest in the M<sub>3</sub> receptor antagonists (Darifenacin, 4-DAMP) in the porcine detrusor. The pA<sub>2</sub> values for four antimuscarinic agents and their rank order seemed to be similar to those in previous reports. Adding together the results of the human detrusor, it was considered that pilocarpine induces urinary bladder contractility via M<sub>3</sub> receptor. The clinical study showed that pilocarpine improved voiding symptoms subjectively and objectively. There was no serious adverse event by this drug.

### Concluding message

Pilocarpine hydrochloride was effective on contraction of porcine and human urinary bladder, and in addition, effective and safe for the treatment of detrusor underactivity.

### Disclosures

**Funding:** none **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Pig **Ethics Committee:** Ethics committee of Dokkyo Medical University