

THE POSSIBLE ACTIONS OF M1, ONE OF METABOLITES OF PROPIVERINE HYDROCHLORIDE, ON BLADDER CONTRACTION

Hypothesis / aims of study

Propiverine hydrochloride is one of the most popular antimuscarinic agents for treatment of overactive bladder in Japan and Korea. It has been suggested that both antimuscarinic and Ca channel blocking effects contribute to the action mechanism of propiverine for inhibition of detrusor overactivity and OAB symptoms. The original propiverine and the three human metabolites have been shown to possess antimuscarinic or calcium channel-blocking properties. After prescription of propiverine, one of the metabolites; l-methyl-4-piperidyl diphenylpropoxyacetate N-oxide (M1) exits in the blood in about 5 to 10 times higher concentration, as compared to the original propiverine. It has been reported that M1 has Ca channel blocking effects, and that this metabolite may have an important role on inhibition of detrusor contraction. Therefore, in the present study, we have evaluated the effects of M1 on isolated human bladder smooth muscles and pelvic nerve stimulation-induced bladder contraction in anesthetized rats.

Study design, materials and methods

Human urinary bladders (7 male and 1 female) were obtained from patients undergoing radical cystectomy due to bladder carcinoma. Smooth muscle strips were dissected from the body of urinary bladders. Each strip was suspended in an organ bath filled with Krebs-Henseleit solution, connected to a force displacement transducer, and isometric force was recorded and monitored on an electronic pen recorder. The effects of M1, propiverine and tolterodine on the contractions induced by carbachol (CCh), 80 mM KCl, and EFS were evaluated. In rats, the lower abdominal cavity was opened with an abdominal mid-line incision, and the pelvic nerves were sectioned bilaterally at the central end of the pelvic plexus. The peripheral end of one of the pelvic nerves was placed on a bipolar platinum electrode, and electrical stimulation of pelvic nerve was applied. To measure the detrusor pressure, a 20 G cannula was transurethrally inserted into the bladder, and was connected in an electronic pressure transducer, and monitored on electronic pen recorder. The effects of intravenous injection of M1, propiverine and tolterodine on the pelvic nerve stimulation-induced bladder contractions were evaluated.

Results

Propiverine (0.1 μ M – 10 μ M) and tolterodine (0.01 μ M – 1 μ M) caused concentration dependent rightward shifts in the concentration response curves for CCh. Although M1 did not have significant effect on the concentration response curves for CCh, M1 significantly reduced the maximum contraction by CCh. M1 (10 μ M) and propiverine (10 μ M) caused significant inhibitions on 80 mM KCl-induced contraction by 35.8% and 33.5%, respectively. However, tolterodine (1 μ M) did not affect KCl-induced contraction. Although tolterodine did not have inhibitory effect on atropine-resistant part of the EFS-induced contraction in human bladder strips, M1 and propiverine caused significant inhibition in the atropine-resistant contraction. Pelvic nerve stimulation caused bladder contraction. The contraction was divided into two components; the first phasic component and the second sustained tonic component. The phasic component was significantly inhibited by treatment of α , β -methylene ATP, and the second tonic component was significantly suppressed by atropine treatment. Intravenous injection of propiverine (1 - 5 mg/kg) caused concentration-dependent inhibitions in both phasic and tonic contractions induced by pelvic nerve stimulation in rats. Tolterodine caused significant inhibition only in the tonic contraction, while, M1 significantly inhibited the phasic contraction only.

Interpretation of results

The present data suggest that M1, one of metabolites of propiverine, has Ca channel blocking action and causes inhibition in atropine-resistant part of contraction in human bladder strips, which is the purinergic component of bladder contraction. Three agents showed different

effects on the pelvic nerve stimulation-induced bladder contraction in rats. The difference may be dependent on the difference in the relative potency between antimuscarinic (cholinergic) and Ca channel blocking (purinergic) action of each agent.

Concluding message

M1, one of the metabolites of propiverine, has Ca channel blocking effects and shows inhibitory effects on detrusor contraction. It is suggested that this metabolite may have an important role for treatment of overactive bladder.