265

Yusup A [1], Akino H [1], Miwa Y[1], Oyama N[1], Aoki Y [1], Tanase K [1], Ishida H [1], Yokoyama O[1]
1. Department of Urology, Faculty of Medical Science, University of Fukui

ANTIMUSCARINIC AGENT EASILY PENETRATING BBB MAY REDUCE VOIDING EFFICIENCY

Hypothesis / aims of study

We previously suggested that the M2 muscarinic receptor in the brain stem contributed to excitatory control of the micturition reflex (1). Antimuscarinic agents, which are widely used to treat overactive bladder (OAB), have well-known effects on peripheral muscarinic receptors. However, some currently used drugs may affect muscarinic receptors in the brain, especially in patients who have had cerebrovascular accidents (CVA) that destroy the blood-brain barrier (BBB). We tested the influences of atropine's easy penetration of BBB, as well as the influences of propiverine's low potential to cross the BBB, on OAB caused by cerebral infarction (CI). We also compared the effects of each drug between intravenous (iv) and intracerebroventricular (icv) administration.

Study design, materials and methods

The tube implantation for iv or icv administration and the left middle cerebral artery occlusion (MCAO) were performed in female SD rats under halothane anesthesia. The cystometrographic effects of iv ($2x10^{-1}$ to $2x10^{3}$ μM) or icv (10^{-2} to 10 nmol) administration of atropine, propiverine, or vehicle were investigated in conscious, sham-operated (SO) and CI rats. Bladder capacity (BC) was defined as the sum of the voided volume (VV) and residual volume (RV). The rats were positioned in a stereotaxic frame under urethane anesthesia. A bilateral small craniotomy was performed to insert a stainless steel cannula into the dorsal pontine tegmentum (DPT). Atropine (14 nmol) was injected into the DPT bilaterally.

Results

In CI rats, BC was markedly reduced after MCAO and remained consistently below half of the pre-occlusion capacity. Propiverine significantly increased VV dose-dependently in CI rats, but had no effect on VV in SO rats. Propiverine did not increase RV, whereas atropine markedly increased it, probably due to the observed decrease in bladder contraction pressure (BCP). The atropine-induced increase in BC was attributable almost entirely to RV. The percent increases in BC and RV, as well as the decrease in BCP, were significantly higher in CI rats than in SO rats. Icv administration of atropine significantly increased RV in both SO and CI rats. The percent changes in BCP in response to icv propiverine and atropine were small, remaining within plus or minus 20% in both CI and SO rats. Atropine decreased the bladder contraction time. Bilateral administration of atropine into the DPT markedly increased RV. However, the decrease in BCP was small.

Interpretation of results

Atropine, like propiverine, is known as a nonselective muscarinic receptor antagonist. The brain concentration of radioactivity 30 minutes after intravenous injection of ^{3}H-atropine is reportedly the same as that in plasma (2). Atropine penetrates the BBB, increasing its potential influence on the brain resulting from muscarinic antagonists after intravenous administration. Icv administration of atropine increased RV provably through inhibition of excitatory contribution of the DPT muscarinic sytem to the micturition reflex. Propiverine's penetration through the BBB is reportedly very low. Propiverine increased BC without increase in RV provably through inhibition of peripheral muscarinic receptors.

Concluding message

The present study suggests that antimuscarinic agents with low potential to cross the BBB are useful for the treatment of OAB caused by CI. Antimuscarinic agents in the brain decrease voiding efficiency probably by suppressing the muscarinic excitatory systems in the DPT.

References

1. Neuropharmacol 41: 629-638, 2001
2. Eur J Pharmacol 20: 224-230, 1972