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COMPARATIVE STUDY OF THE EFFECTS OF ZD0947 AND TOLTERODINE ON BLADDER FUNCTION IN A PARAPLEGIC RAT MODEL

Hypothesis / aims of study

The well-known side effects of antimuscarinic drugs have focused interest on other ways of treating overactive bladder. Our aim was to compare the effects of tolterodine and ZD0947 (a novel ATP-sensitive potassium channel opener) on bladder function in a paraplegic rat model.

Study design, materials and methods

Sprague-Dawley rats (n=102) were studied with 6 animals as normal controls and 96 subjected to spinal cord transection (SCT) at the 10^{th} thoracic vertebrae. Two weeks after SCT, 6 animals were evaluated with filling cystometrography (CMG) to confirm development of detrusor hyperreflexia (DH), while 24 animals were used as vehicle controls. The remaining animals were used to evaluate the efficacy of tolterodine and ZD0947 on filling CMG parameters. Animals were divided into equal groups (n=6). Drugs were administered as i) 3 µmol/kg by gavage for one and two weeks, ii) 10 µmol/kg by gavage for one and two weeks, or as iii) 1 µmol/kg subcutaneously (Alza miniosmotic pumps) for continuous delivery throughout one and two weeks.

Results

3 µmol/kg po: On average ZD0947 decreased the incidence of DH compared with tolterodine and vehicle controls after one and two weeks of treatment. This change was associated with decreased frequency of DH contractions compared to tolterodine and vehicle control groups ($p<0.05$). Each drug reduced the amplitude of DH, with the greatest effect caused after two-week administration of ZD0947 ($p<0.05$). Bladder capacity was increased after one-week exposure to ZD0947. Administration of ZD0947 did not change basal bladder pressure or maximum developed bladder pressure.

10 µmol/kg po: ZD0947 and tolterodine decreased the incidence of DH compared to vehicle controls with a rank order for improvement after two weeks of ZD0947 > tolterodine. ZD0947 decreased the frequency of DH contractions (0.38±0.22 contraction/minute) after two-week drug administration, and the effect was greater than tolterodine (0.91±0.28 contraction/minute). The amplitude of DH contractions with the drugs was comparable to vehicle controls, whereas bladder capacity was relatively unaffected. There was no significant change in maximum developed bladder pressure with either drug.

1 µmol/kg sc: Both ZD0947 and tolterodine improved the incidence of DH, and decreased the frequency and amplitude of DH compared to vehicle controls. This decrease was most remarkable with Tolterodine ($p<0.05$). Bladder capacity was increased with ZD0947 and tolterodine whereas basal bladder pressure and maximum developed bladder pressure did not change in response to treatment with either drug.

Concluding message

ZD0947 is a promising new pharmacological agent for the treatment of DH.

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