Bladder and Urethra: Anatomy, Physiology & Pharmacology

Discussed Poster
Sunday, May 21, 2006 9:00 am - 12:00 pm

195

EFFECTS OF A COMBINED 5HT3 RECEPTOR ANTAGONIST AND NORADRENALINE REUPTAKE INHIBITOR ON LOWER URINARY TRACT ACTIVITY

Matthew O Fraser, China Chien, Mary A Katofiasc, Christopher L Langdale, Jacqueline D Brooks, Melissa C Young, Kenneth J Olejar, Venkateswarlu Karicheti, Karl B Thor, Durham, NC*

Introduction and Objective: The involvement of serotonin in the central control of lower urinary tract function (LUT) is well established, but the role of the 5HT3 receptor has been controversial. This is in contrast to the well established role of 5HT3 receptors in the gut, where they are undeniably involved both peripherally and centrally in both pain sensation and motility. Like serotonin, the involvement of noradrenaline in LUT function is well established both centrally and peripherally. DDP225 (a.k.a. MCI-225) is a combined 5HT3 receptor antagonist and noradrenaline reuptake inhibitor (NARI) and has been demonstrated to work well in models of irritable bowel syndrome. We tested whether this particular mix of properties make this compound useful for overactive bladder (OAB) with and without pain components. Methods: For cystometric evaluation, anesthetized female SD rats (n=8) and anesthetized female cats (n=4) underwent continuous transvesical cystometry before and after irritation with dilute acetic acid infusion. Cumulative doses of DDP225 from 1-30 mg/kg at half log intervals were administered following vehicle controls. Bladder capacity (BC) was estimated at each treatment by single filling cystometry. In order to determine the effects of sub-chronic oral dosing on bladder function, normal cats (n=6) were fitted with indwelling catheter-pressure transducer telemetry units that allowed 24 hour measurement of bladder pressure and simultaneous urine collection in a metabolic cage-style setup. Following a control recording week, the cats were dosed with DDP225 on consecutive days b.i.d. with 0, 1, 3 and 10 mg/kg orally. Functional bladder capacity (FBC) and bladder contraction areas under the curve (AUC) were calculated. Data were analyzed by repeated measures ANOVA. Results: Administration of DDP225 in anesthetized animals resulted in a significant dose-dependent reversal of acetic acid-induced bladder irritation in both the rat (35%, $P<0.0001$) and the cat (25%, $P=0.0379$). Moreover, DDP225 at 10 mg/kg orally resulted in a >150% increase in FBC ($P=0.0188$) with no change in AUC, with no obvious untoward side-effects. Conclusions: These results with DDP225 suggest that the mix of 5HT3 antagonism and NARI activities provides preclinical efficacy in multiple species and widely variant models for the study of LUT function. Further, these results suggest that such an approach may be utilizable for the treatment of lower urinary tract disorders ranging from interstitial cystitis through idiopathic OAB.

Source of Funding: Internal