575

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EFFECTS OF NON- AND SELECTIVE CYCLOOXYGENASE INHIBITORS ON ACETIC ACID-EVOKED BLADDER IRRITATION IN THE ANAESTHETIZED FEMALE CAT

Hypothesis / aims of study

Previous studies have demonstrated a role for prostaglandins produced via the cyclooxygenase (COX) pathway in the physiological regulation of the micturition reflex. Non-selective COX inhibitors increase bladder capacity in bladder models, independent of chemical bladder irritation (1,2). However, reports on the effects of selective COX-2 inhibitors on bladder function have been conflicting. Furthermore, there are no reports on the effects of selective COX-1 inhibitors on micturition, and the role of COX isozymes in micturition in the cat has not been studied. Thus, the present study investigated the effects of non-selective and isozyme selective COX inhibitors on acetic acid-evoked bladder irritation in the female cat.

Study design, materials and methods

Experiments were performed on adult female cats anaesthetized with alpha-chloralose (50 – 75 mg/kg i.v.). A cannula was inserted into the bladder dome, secured with a purse sting suture and the bladder was infused with saline (0.5 ml/min) to evoke the micturition reflex. Control reflex parameters were obtained (voided volume, residual volume, bladder capacity) and drug administered (intravenous, i.v.). Intravesical saline infusion was replaced with dilute acetic acid (0.7 %) and infused into the bladder to evoke irritation. Acetic acid-evoked effects on void function were expressed as percentage changes from control parameters, and drug or vehicle effects on bladder irritation compared by two-way Anova followed by Bonferroni post-test.

Results

Bladder infusion of acetic acid in vehicle-treated cats resulted in a decrease in bladder capacity of 30 $\pm$ 9 %. Indomethacin, ibuprofen and ketoprofen (0.3 mg/kg i.v.), non-selective COX inhibitors, all significantly increased bladder capacity (maximum increases of 121 $\pm$ 33 %, 70 $\pm$ 36 % and 58 $\pm$ 15%, respectively), and therefore inhibited acetic acid-evoked irritation. Indomethacin and ketoprofen had no effect on voided or residual volume, whereas ibuprofen evoked a significant increase in residual volume (maximum increase 450 $\pm$ 178 %). The highly selective COX-1 (FR-122047) and COX-2 inhibitors (NS-398, DuP697 and nimesulide) had no significant effects on void function at high doses (3 mg/kg i.v.).

Interpretation of results

The results of the present study suggest that blockade of both COX-1 and COX-2 is required to produce urodynamic changes in the anaesthetized cat. Furthermore, pre-treatment with selective COX-1 and COX-2 inhibitors has no effect on bladder instability evoked by intravesical acetic acid in this species.

Concluding message

Dual COX-1 and COX-2 inhibition evokes an increase in bladder capacity in acetic acid-evoked bladder irritation in the anaesthetized female cat. Selective COX-1 and COX-2 pre-treatment has no effect on the bladder instability evoked by intravesical acetic acid in this species.

References

(1) Pharmacological evaluation of the role of cyclooxygenase isoenzymes on the micturition reflex following experimental cystitis in rats (200). BJP., 130(2), 331-338
(2) The effect of cyclooxygenase inhibitors on the low filling rate cystometrogram in urethane anesthetized rats (1985). J.Urol., 134(4), 800-803.