Pharmacokinetics and pharmacokinetic/pharmacodynamic modelling of robenacoxib and ketoprofen in a carrageenan-induced inflammation model in the cat

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Session 14 Pain and Inflammation: Wednesday 11-07: 16.00 – 18.00

14.2. Pharmacokinetics and pharmacokinetic/pharmacodynamic modelling of robenacoxib and ketoprofen in a carrageenan-induced inflammation model in the cat

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Introduction: Robenacoxib and ketoprofen are non-steroidal anti-inflammatory drugs (NSAIDs) licensed for once daily administration in cats, despite their rapid clearance from blood.
Objective: We hypothesised that robenacoxib (COX-2 selective) and ketoprofen (COX-1 preferential) would exert anti-inflammatory effects of similar duration and intensity in carrageenan-induced inflammation.
Materials and Methods: Eight cats (1 to 3yo) weighing 4.0±0.39 kg were enrolled in a randomised, placebo controlled, three period cross-over study (28 days wash-out). In each period, 1.0 mL of a 2% sterile lambda carrageenan solution was injected into a subcutaneously implanted tissue cage. Robenacoxib (2 mg/kg), racemic ketoprofen (2 mg/kg) or a placebo formulation was administered subcutaneously. Blood samples were taken from indwelling jugular catheters at pre-determined times for NSAID and serum thromboxane(Tx)B_2 (1 h incubation, 37°C) measurements. Tissue cage exudate samples (1mL) were obtained before and at pre-determined times (up to 120 h) after carrageenan injection for determination of robenacoxib and prostaglandin(PG)E_2 concentrations. Exudate PGE_2 generation and *ex vivo* serum TxB_2 synthesis inhibition were taken as surrogate markers of COX-2 and COX-1 activity, respectively. Groups were compared using repeated-measurement analysis of variance (SAS PROC MIXED) with main effects for treatment group, time, sex and period. Significance was set at $P<0.05$. Individual time-concentration curves, pharmacokinetic (PK) variables, effect-concentration curves and pharmacodynamic (PD) parameters for COX-1 and COX-2 inhibition were generated by modelling in WinNonlin 5.2. Average PD parameters were obtained by naïve pooled data analysis.
Results: S(+)ketoprofen was rapidly cleared from plasma, as apparent clearance (CL/F) was 0.114 [95% Confidence Interval: 0.092-0.142] L/kg/h and terminal elimination half-life was 1.62±1.14 h. Apparent blood robenacoxib clearance was high (0.684 L/kg/h [95%CI: 0.622-0.753]) and terminal half life was 1.13h±0.18 h. Elimination half-lives from tissue cages were 25.9±3.7 h for S(+) ketoprofen (MRT 35.9 h) and 41.5±8.8 h for robenacoxib (MRT 45.7 h).Both drugs significantly reduced exudate PGE_2 between 6 and 36 h. Maximum exudate PGE_2 inhibitions were 92.1% for robenacoxib and 90.9% for S(+)ketoprofen at 9 h. Ketoprofen significantly suppressed (>97%) serum TxB_2 between 4 min and 24 h, whereas TxB_2 suppression was only transient with robenacoxib (51.2% at 2 h). Geometric mean IC_{50}COX-2 was 48.5 ng/mL (0.191 µM) for S(+)ketoprofen and 38.2 ng/mL (0.117 µM) for robenacoxib. Geometric mean IC_{50}COX-1 was 0.17 ng/mL (0.67×10^{-3} µM) for S(+)ketoprofen and 2950 ng/mL (9.0 µM) for robenacoxib.
Conclusions: The inhibition of COX-2 was similar in magnitude and time course for robenacoxib and ketoprofen, whereas COX-1 inhibition was marked and persistent for ketoprofen only.

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ABSTRACTS