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Safety of oral robenacoxib in the cat

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The safety of robenacoxib, a nonsteroidal anti-inflammatory drug with high selectivity for inhibition of the cyclooxygenase (COX)-2 isoform of COX, was investigated in the cat in two randomized, blinded, placebo-controlled, parallel-group studies. Robenacoxib was administered orally to healthy young domestic short-hair cats at dosages of 0 (placebo), 5 and 10 mg/kg once daily for 28 days (study 1) and at 0 (placebo), 2, 6 and 10 mg/kg twice daily for 42 days (study 2). The recommended minimum dosage for robenacoxib tablets in cats is 1 mg/kg once daily (range 1–2.4 mg/kg). Relative to placebo treatment, no toxicologically significant effects of robenacoxib were recorded in either study, based on general observations of health, haematological and clinical chemistry variables and urinalyses in life, and by *post mortem* organ weight, gross pathology and histopathology assessments. Pharmacokinetic–pharmacodynamic simulations indicated that all dosages of robenacoxib were associated with marked inhibition of COX-2 at peak effect (median I_{max} 97.8–99.4% inhibition) with lesser inhibition of COX-1 (median I_{max} 26.8–58.3% inhibition). Inhibition of the COXs was short lasting, with >10% median inhibition persisting for 4.0 h for COX-2 and 1.5 h for COX-1. These levels of inhibition of COX-1 and COX-2 twice daily with robenacoxib were not associated with any detectable toxicity, suggesting that, as previously described in dogs, the high safety index of robenacoxib in cats may be related to a combination of its high COX-2 selectivity and short residence time in the central compartment.

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INTRODUCTION

Although the need to provide adequate analgesia in the cat has been increasingly recognized (Robertson, 2005, 2008; Lascelles *et al.*, 2007; Livingston, 2010), there are relatively few non-steroidal anti-inflammatory drugs (NSAIDs) licensed for feline use, and their usage is generally limited to administration over short periods of time. For example, carprofen is authorized only for single use, ketoprofen for a maximum of 5 days and tolfenamic acid for a maximum of 3 days. Meloxicam is licensed as a single dose of 0.3 mg/kg subcutaneously in the cat and, in the EU, at a much lower dosage of 0.05 mg/kg orally for long-term therapy of unrestricted duration. Although meloxicam is licensed and recommended for long-term use in the cat (Gunew *et al.*, 2007), the manufacturer's literature indicates that the safety margin in this species is narrow (European Public Assessment Report Scientific Discussion for Metacam, 2010, http://www.ema.europa.eu) and, because of concerns on toxicity, a cautious approach was proposed by Papich (2008) and Robertson (2008).

The small number of NSAIDs licensed for use in the cat, their limited indications and restrictions on duration of dosing may reflect the paucity of pharmacological and toxicological data in the cat together with the low safety margins for many NSAIDs in this species. The poor safety margins of some NSAIDs in cats may be a result of their slow clearance from the body (Lascelles *et al.*, 2007).

In recent years, NSAIDs of the coxib class, which are preferential or selective in their inhibitory action for the cyclooxygenase (COX)-2 isoform, have been developed for canine use (McCann *et al.*, 2005; King *et al.*, 2009; Roberts *et al.*, 2009; Cox *et al.*, 2010). The rationale underlying development of the coxibs is that they should have similar efficacy but improved safety profiles compared with the older nonselective NSAIDs. Five drugs of the coxib class, cimicoxib, deracoxib, firocoxib, mavacoxib and robenacoxib are now

licensed for use in the dog, but only one, robenacoxib, is authorized for administration to cats.

In the cat, dog and rat, robenacoxib has been shown to be a highly selective inhibitor of COX-2 (Giraudel *et al.*, 2009a; King *et al.*, 2009, 2010; Schmid *et al.*, 2010) and possesses the analgesic, anti-inflammatory and antipyretic actions characteristic of NSAIDs (Giraudel *et al.*, 2009b; King *et al.*, 2009). The pharmacokinetic (PK) profile of robenacoxib has been described in the cat and dog following oral and subcutaneous administration (Giraudel *et al.*, 2009b; Jung *et al.*, 2009; Pelligand *et al.*, 2009; J.N. King, M. Jung, M.P. Maurer, V.B. Schmid, W. Seewald & P. Lees, In preparation). In both species, absorption is rapid after oral and subcutaneous dosing, whilst clearance is also rapid and the elimination half-life from blood is short. However, in the cat, dog and rat, robenacoxib has been shown to persist for longer in inflammatory exudate than in blood (King *et al.*, 2009; Pelligand *et al.*, 2009; Silber *et al.*, 2010).

The aim of this study was to complement the reported feline studies on robenacoxib PK and pharmacodynamics (PD), administered at recommended dosages, by investigating the safety profile of robenacoxib in the cat. The principal objective was to investigate the safety of robenacoxib, in a tablet formulation, administered at daily dosages of 0, 5 and 10 mg/kg (28-day study) and 4, 12 and 20 mg/kg (42-day study). As the clinically recommended dosage of robenacoxib is 1–2.4 mg/kg, the 20 mg/kg dosage constitutes an 8.3- to 20-fold overdose. In both studies, safety was assessed by: (i) observations and examinations to establish general health status; (ii) haematology and clinical chemistry profiles; (iii) urinalyses; and (iv) *post mortem* investigations, including gross and histopathology. A second objective was to use Pharmacokinetic-pharmacodynamic (PK-PD) modelling to correlate safety data with the magnitude and time course of inhibition of COX-1 and COX-2 in the central compartment.

MATERIALS AND METHODS

Two safety studies were conducted. In study 1, cats received 0, 5 and 10 mg/kg robenacoxib once daily for 28 days at Liberty Research Inc. (Waverly, NY, USA). In study 2, cats received 0, 2, 6 and 10 mg/kg robenacoxib twice daily for 42 days at Novartis Centre de Recherches (St Aubin, Fribourg, Switzerland). Both studies were run in compliance with GLP and site procedures, FDA Guidelines on the conduct of target animal safety studies (CVM Guidelines 33 and 104), and after approval of the protocol by institutional Animal Use and Welfare Committees.

Animals

Healthy young domestic short-hair cats were used. All cats were in good health at the start of the study as assessed by physical examinations plus haematological, clinical chemistry and urinalyses. The acclimatization phase for the cats was approximately 2 weeks in study 1, and 3 weeks in study 2.

In study 1, nine females and nine males were used, aged 20–21 weeks with average body weights of 2.4 kg (females) and 2.8 kg (males) at study commencement. In study 2, 16 females and 16 males were used, aged 7.5–8.5 months with average body weights of 2.8 kg (females) and 3.7 kg (males) at study commencement.

Cats were housed in environmentally controlled rooms with regulation of temperature and relative humidity. The light:dark cycle was 12 h:12 h in study 1 and 14 h:10 h in study 2. In study 1, cats were housed in individual cages. In study 2, cats were group housed during the day but were housed individually at night and during sampling periods. The cats were fed certified Feline Diet 5003 (PMI Nutrition International, St. Louis, MO, USA) *ad libitum*, renewed once daily, in study 1, and Selina® 3-mix (A/S Arovit Petfeed, Denmark-6600 Vejen, Denmark) provided twice daily in study 2. In both studies, fresh drinking water was available *ad libitum*. Feed consumption was measured once daily in study 1 and twice daily in study 2. Body weight was recorded weekly in both studies.

Baseline values (including body weight and clinical observations) before the start of dosing with the test articles were recorded for 14 days in study 1, and 12–13 days in study 2.

Study designs

In both studies, prospective, randomized, blinded, parallel-group designs were used. Cats were assigned to treatment groups with three groups each of six cats (three female, three male) in study 1, and four groups each of eight cats (four female, four male) in study 2. Randomizations were conducted separately for females and males with additional stratification by weight within sex to ensure that cats spanning the range of body weights of both genders were represented in each group.

In both studies, there was a separation of responsibilities, such that personnel conducting the clinical observations, physical examinations, clinical pathology and gross and microscopic pathology were blinded to the treatment each cat received. As there were 32 cats in study 2, not all procedures could be managed within a single day. Therefore, some procedures were spread over 2–3 days (e.g., 3 days for the *post mortems*).

Test articles

In study 1, cats received nonflavoured lactose-based tablets containing 10 mg robenacoxib, or matched placebo tablets identical in composition to the robenacoxib tablets but excluding the active ingredient (Novartis Animal Health, Basel, Switzerland). Cats were dosed once daily with 5 mg/kg robenacoxib (Group B), 10 mg/kg robenacoxib (Group C) or placebo (Group A), administered in an amount equivalent to the 10 mg/kg robenacoxib group. Combinations of whole or half tablets were placed on the back of the tongue, and the mouth held closed until the tablets were swallowed. All cats were treated for 28 consecutive days. As food was available *ad libitum*, the relation between feed intake and test article administered was not controlled.

In study 2, cats received flavoured tablets containing 6 mg of robenacoxib (Onsior®; Novartis Animal Health). Cats were dosed

twice daily with robenacoxib at dosages of 2, 6 and 10 mg/kg (in Groups B, C and D, respectively) or placebo (Group A). For dosing, whole or parts of tablets were placed into hard gelatine capsules (Dermarcam S.A., Chambesy, Switzerland). The placebo comprised an empty gelatine capsule. Each capsule was placed on the back of the tongue and the cats administered a small volume of tap water to facilitate swallowing. Treatments were given twice daily for 42–44 consecutive days. The cats were fed twice daily 1 h after the administration of the test articles (8.00–10.00 and 18.00–20.00).

Safety variables recorded and samples collected in life

Cats were observed twice daily for general health and behaviour. In addition, each cat had a detailed physical examination by a veterinarian on two occasions in study 1 (in the baseline period and on day 21 of dosing) and on three occasions in study 2 (at the start of acclimatization, in the baseline period and in week 4 of treatment).

Venous blood samples were taken (from a jugular vein in study 1 and from a cephalic or brachial vein in study 2) for blood haematology and coagulation and serum clinical chemistry analyses. In study 1, blood samples were taken prior to drug dosing and again at the end of the dosage period, with no record of relation to feeding. In study 2, samples were collected from fasted animals on days −13/−12, −7/−6, 14/15 and 35/36. Anticoagulants were EDTA for haematology and sodium citrate for coagulation variables. No anticoagulant was used for serum chemistry variables. Variables measured included serum alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), alkaline phosphatase, creatinine kinase, gamma-glutamyltransferase (GGT), bilirubin, creatinine, urea (blood urea nitrogen), glucose, calcium, chloride, inorganic phosphorus, potassium, sodium, total protein, albumin and globulin. Haematology variables included erythrocyte count, haemoglobin concentration, haematocrit, mean cell volume, platelet count, total leucocyte count, differential counts for neutrophils, eosinophils, basophils, monocytes and lymphocytes, and activated partial thromboplastin time.

Urine samples were collected on the same days as the blood samples in study 1, and on days −13/−12/−11, −6/−5, 13/14/15 and immediately prior to necropsy on days 42/43/44 in study 2. Urine was collected via free catch into litter trays except after euthanasia, when it was collected directly with a syringe and needle from the bladder. Variables measured included urine pH and urine-specific gravity.

Blood robenacoxib concentrations

In study 2, blood samples for measurement of robenacoxib concentration were taken from a cephalic vein into EDTA on days −12, −7 and 35. The 35 day samples were collected immediately before the a.m. dosing, i.e., approximately 12 h after the previous dose. Blood samples were stored below −16 °C before determination of blood robenacoxib concentrations using a liquid chromatography–mass spectrometry method as described and validated previously in cats (Jung *et al.*, 2009). The limit of quantification in cat blood was 3 ng/mL.

Variables recorded post mortem

In study 1, after 28 days dosing, the animals were fasted overnight, anaesthetized with ketamine (Fort Dodge Animal Health, Overland Park, KS, USA) and then euthanized with pentobarbital (Fort Dodge Animal Health), both drugs administered intravenously. In study 2, after 42–44 days of treatment, cats were euthanized by intravenous injection of pentobarbital (Esconarkon®; G. Streuli and Co., Uznach, Switzerland). The cats were then exsanguinated and necropsies performed, together with organ weight measurements and macroscopic and histopathology on a wide range of tissues. Selected organs and tissues collected for weighing and histopathological investigation are indicated in the Results section (*vide infra*, not all data shown). All tissues were preserved in 10% formalin (study 1) and neutral phosphate-buffered formalin (study 2) except for testes, epididymides and eyes with optic nerves, which were fixed in Davidson's solution.

Statistical analyses of safety studies

Data are reported as mean and SD. Data for most variables were numerical and were analysed statistically by analysis of variance (ANOVA) using SAS® procedure PROC MIXED (SAS® Institute Inc, Cary, NC, USA). ANOVA was used for endpoints measured post-treatment only once, and repeated measures analysis of variance (RMANOVA) for endpoints measured multiple times post-treatment. Analysis of covariance (RMANCOVA) was used for variables with a baseline value and multiple measures post-treatment. Data were log (study 2) or rank (study 1) transformed if required to give the best estimation of a normal distribution. The following parameters were included in the original ANOVA models: treatment, sex, treatment × sex interaction, block and baseline (if applicable). For RMANOVA and RMANCOVA, time and treatment × time interaction were included also. Nonsignificant terms were removed sequentially from the model. In the event of overall significance, groups were compared with the placebo group in *post hoc* analyses using linear contrasts with correction for multiple tests, either for pooled sexes (if the treatment × sex interaction was not significant) or separately for each sex (if the interaction was significant).

All calculations were carried out using the software SAS®, Versions 8.2. (study 1) and 9.1.3. (study 2) (SAS® Institute Inc). Two-tailed P values less than 0.05 were considered significant.

PK–PD simulations

Pharmacokinetic–pharmacodynamic simulations were undertaken using: (i) blood concentration–time data generated in a previous investigation in 12 cats (six male, six female), in which dosages of 1–2 mg/kg robenacoxib were administered orally to each cat on a single occasion in a cross-over study to investigate the effect of feeding on PK variables (study 3, J.N. King, M. Jung,

M.P. Maurer, V.B. Schmid, W. Seewald & P. Lees, In preparation); and (ii) PD data generated in another previous investigation that established IC_{50} values for inhibition of COX-1 and COX-2 isoforms in the cat (study 4, Giraudel *et al.*, 2009a). Total blood concentrations of robenacoxib were used in the analysis because, although binding to plasma proteins is extensive (>99%), this binding is linear (Jung *et al.*, 2009). As oral bioavailability of robenacoxib is higher when cats are fasted, simulations were calculated for fasted animals (J.N. King, M. Jung, M.P. Maurer, V.B. Schmid, W. Seewald & P. Lees, In preparation). A total of 12 robenacoxib concentration–time profiles were available from fasted cats. To standardize profiles, blood concentrations were adjusted to a nominal dose of 1 mg/kg, assuming linear PKs. A one-compartment PK model was fitted to each of the 12 concentration–time profiles as follows with parameters: FD/V = absorbed dose/volume of distribution, K_{10} = rate constant for elimination and K_a = rate constant for absorption, with $K_a \geq K_{10}$.

Blood concentration (C) is given by:

$$C = \frac{FD}{V} \times \frac{K_a}{K_a - K_{10}} \times [\exp(-K_{10} \times t) - \exp(-K_a \times t)], \quad \text{if } K_a > K_{10}$$

$$C = \frac{FD}{V} \times K_{10} \times t \times \exp(-K_{10} \times t), \quad \text{if } K_a = K_{10}$$

Fitting parameters involved optimizing a nonlinear function, which was conducted iteratively. Only good model fits (n = 10) were used subsequently. The data did not always conform, so it was assumed pragmatically that $K_a = K_{10}$, which, for most of the profiles, was in fact the case. Consequently, only two of the three parameters, FD/V and $K_{10,}$ remain. To obtain the approximate distributions of these two parameters from the 10 pairs of values obtained, the data were re-parameterized. Natural parameters were considered to be volume of distribution (V) and $AUC = \frac{FD}{V} \times K_{10}$, or logarithms thereof. Univariate inspection of these parameters showed that log V and log AUC followed approximately a Gaussian distribution, although both seemed to be correlated. Therefore, a bivariate Gaussian distribution (with nonzero correlation) was fitted to the 10 pairs of values (log AUC, log V). For dosages other than 1 mg/kg, AUC was multiplied by the dosage.

For PD data, the standard sigmoidal (Hill) model

$$\% \text{ inhibition} = \frac{I_{max} \times C^n}{IC_{50}^n + C^n}$$

was used to establish predicted profiles of inhibition of thromboxane $(Tx)B_2$ (COX-1) and prostaglandin $(PG)E_2$ (COX-2) with dosages of 2, 6 and 10 mg/kg of robenacoxib. I_{max} represents the maximal inhibition, C the (total blood) concentration of robenacoxib, IC_{50} the concentration of robenacoxib providing 50% of I_{max}, and n the slope parameter. Geometric mean (geometric SD) values for n and IC_{50} (ng/mL) were, respectively, 0.79 (1.48) and 7298 (2.17) for inhibition of TxB_2, and 0.89 (1.56) and 21.0 (2.49) for inhibition of PGE_2 (study 4, Giraudel *et al.*, 2009a).

For simulations in 10 000 animals, values for log $V_{D,}$ log AUC, n (TxB_2), log ED_{50} (TxB_2), n (PGE_2) and log ED_{50} (PGE_2) were drawn randomly from their underlying distributions (taking into account the correlations). Blood concentrations of robenacoxib and corresponding inhibitions of TxB_2 and PGE_2 were calculated using the underlying models. Medians and 90% tolerance intervals were calculated and plotted against time. All calculations were carried out using the software SAS®, Version 9.1.3. (SAS® Institute Inc).

RESULTS

Study 1

Nominal dosages were 0, 5 and 10 mg/kg robenacoxib once daily, respectively, in groups A, B and C. Actual daily dosages received by Groups B and C over the 28 day dosing periods were respectively: 5.43 ± 0.09 mg/kg (males) and 5.53 ± 0.12 mg/kg (females) in Group B; and 10.35 ± 0.25 mg/kg (males) and 10.44 ± 0.28 mg/kg (females) in Group C.

No cat died or became moribund during the study. Based on clinical observations of general health [appetite, behaviour, body temperature and integument, and cardiovascular (heart rate), gastrointestinal, muscular, nervous, respiratory (respiratory rate) and ocular systems], there were no statistically significant or toxicologically relevant changes either from baseline measurements or for the comparisons of robenacoxib with placebo-treated cats (data not shown). The commonest sign was soft stools, which occurred in a maximum of two of six cats per group. Body weight increased in all groups each week throughout the study in both females and males, with the following exceptions: slight decrease of 0.02 kg between days 21 and 27 (Group C females); slight decrease of 0.01 kg between days 21 and 27 (Group B males); and no change in weight between days 21 and 27 (Group C males). For pooled sexes data, there were no significant differences between the placebo- and robenacoxib-treated groups for body weight. However, mean body weight gain was significantly lower for Group C in the first week of dosing compared with the gain achieved in the preceding week. As the rate of gain in weight in this group was similar to historical data in the colony, it was concluded to be unrelated to treatment.

Mean daily food consumption was not significantly different in each week of the study between treatment groups with one exception. During week 2, food consumption was statistically lower compared with other weeks for Group C cats. As this occurred in a single week only, it was not considered to be toxicologically relevant.

Summary data for selected haematology variables are presented in Table 1 (not all data shown). There were no significant differences in predosing (day 0) values for any variable between the placebo group and either the 5 or 10 mg/kg robenacoxib groups. By day 28, there were significant increases in

Table 1. Summary of haematology data for cats in study 1; mean (SD), $n = 6$

Variable (units)	Day	Group A (placebo)	Group B (robenacoxib 5 mg/kg)	Group C (robenacoxib 10 mg/kg)
Erythrocyte count (10^{12}/L)	0	8.1 (1.2)	7.7 (0.9)	8.2 (0.8)
	28	8.4 (1.1)	8.8 (1.2)**	9.0 (0.8)*
Haemoglobin concentration (mM)	0	11.2 (1.3)	10.1 (1.3)	10.9 (0.9)
	28	11.5 (1.1)	11.3 (1.5)*	11.7 (0.6)
Haematocrit (L/L)	0	0.34 (0.04)	0.31 (0.04)	0.33 (0.03)
	28	0.34 (0.04)	0.34 (0.05)*	0.35 (0.03)
Platelet count (10^9/L)	0	221.3 (127.8)	233.3 (120.0)	315.0 (133.7)
	28	207.3 (126.7)	247.3 (171.6)	274.5 (125.9)
Total leucocyte count (10^9/L)	0	12.3 (5.2)	14.7 (4.9)	14.3 (4.9)
	28	7.1 (2.0)	11.3 (3.7)*	9.7 (2.0)
Activated partial thromboplastin time (sec)	0	49.7 (11.8)	56.4 (13.3)	53.7 (7.2)
	28	60.1 (22.9)	59.9 (7.2)	52.5 (8.4)

Statistical difference between placebo and robenacoxib-treated cats: *$P < 0.05$; **$P < 0.01$.

erythrocyte count, leucocyte count, monocyte count and haematocrit, and a significant reduction in haemoglobin concentration in the 5 mg/kg robenacoxib group (Group B) compared with placebo (Group A). From the small magnitude of the changes, the differences were considered to be not relevant toxicologically. Moreover, comparison between cats receiving 10 mg/kg robenacoxib (Group C) and placebo revealed only one statistically significant difference, a numerically slight increase in erythrocyte count.

Summary data for selected clinical chemistry variables are presented in Table 2 (not all data shown). There were no significant differences in predosing (day 0) values for any variable between the placebo group and either the 5 or 10 mg/kg robenacoxib groups. By day 28, there were statistically significant increases in total protein, albumin and globulin concentrations in cats receiving 5 mg/kg robenacoxib (Group B) compared with placebo (Group A). In each case, the changes were numerically small, and similar changes compared with placebo were not obtained in cats administered 10 mg/kg robenacoxib (Group C). There were significant, but numerically small, reductions in inorganic phosphorus concentration by day 28 in both robenacoxib groups relative to placebo. None of the clinical chemistry differences were considered to be toxicologically relevant.

Urine was examined visually for appearance and microscopically for formed elements and analysed for specific gravity. There were no significant differences between placebo and robenacoxib groups on either day 0 or day 28.

Gross pathology examinations revealed occasional findings in all groups, but these did not follow any pattern that would indicate a relationship to treatment or differences between groups. These comprised small testes and thymus, enlarged thyroid, cervical lymph nodes and ovary, small nodule on pancreas, small discoloration on spleen and enlarged and/or mottled lymph nodes.

Initial and final body weights and *post mortem* organ weights are presented in Table 3. There were no significant differences between groups. Organ weights were also expressed (i) as a percentage of body weights and (ii) as a percentage of brain weights. Apart from a significant increase in pituitary/body weight ratio and pituitary/brain ratio in Group B, there were no

Table 2. Summary of serum clinical chemistry data for cats in study 1; mean (SD), $n = 6$

Variable (units)	Day	Group A (placebo)	Group B (robenacoxib 5 mg/kg)	Group C (robenacoxib 10 mg/kg)
Alanine aminotransferase (IU/L)	0	49.3 (6.8)	59.8 (10.5)	55.3 (6.6)
	28	62.7 (7.9)	74.2 (13.7)	56.7 (12.2)
Aspartate aminotransferase (IU/L)	0	26.3 (3.3)	23.2 (2.4)	25.2 (2.0)
	28	22.5 (2.9)	23.7 (1.9)	20.2 (4.9)
Creatine kinase (IU/L)	0	629.5 (165.8)	401.5 (45.9)	435.3 (186.6)
	28	402.3 (134.4)	593.0 (264.3)	464.7 (75.1)
Alkaline phosphatase (IU/L)	0	131.0 (57.5)	142.7 (37.0)	116.8 (38.0)
	28	117.5 (32.5)	124.3 (38.3)	92.0 (32.2)
Blood urea nitrogen (mM)	0	5.1 (1.2)	4.6 (0.8)	5.1 (0.8)
	28	4.3 (0.9)	4.2 (0.8)	4.0 (0.8)
Creatinine (μM)	0	63.4 (17.2)	56.0 (7.2)	64.9 (10.7)
	28	84.1 (14.5)	76.7 (16.5)	88.5 (12.5)
Total protein (g/L)	0	63.7 (4.3)	62.7 (2.5)	64.0 (3.2)
	28	61.8 (2.6)	64.5 (3.9)*	62.7 (2.3)

Statistical difference between placebo and robenacoxib-treated cats: *$P < 0.01$.

Table 3. Summary of body (kg) and organ (g) weights in cats in study 1; mean (SD), $n = 6$ unless stated

Organ	Group A (placebo)	Group B (robenacoxib 5 mg/kg)	Group C (robenacoxib 10 mg/kg)
Initial bodyweight	2.6 (0.3)	2.6 (0.3)	2.6 (0.3)
Final bodyweight	3.0 (0.4)	3.0 (0.4)	2.9 (0.4)
Heart	13.0 (2.4)	12.9 (2.9)	12.5 (1.4)
Kidneys	20.8 (3.8)	22.1 (5.2)	19.4 (4.4)
Liver	85.4 (15.5)	90.8 (19.9)	83.2 (16.8)
Thymus	7.0 (1.0)	5.5 (2.4)	5.7 (1.5)
Spleen	11.5 (2.7)	9.9 (2.9)	10.9 (5.2)
Ovaries ($n = 3$)	0.46 (0.1)	0.46 (0.1)	0.41 (0.1)
Uterus with cervix ($n = 3$)	3.9 (0.5)	2.9 (2.0)	2.7 (0.9)
Testes ($n = 3$)	1.4 (0.4)	1.8 (1.1)	1.2 (0.5)
Thyroid	0.39 (0.08)	0.74 (0.6)	0.61 (0.56)
Adrenals	0.41 (0.05)	0.42 (0.1)	0.40 (0.08)
Pituitary	0.035 (0.01)	0.050 (0.02)	0.038 (0.016)
Brain	26.0 (3.8)	26.2 (1.6)	27.2 (2.8)

Differences between placebo and robenacoxib-treated cats were not statistically significant.

significant differences between placebo and robenacoxib groups (data not shown).

Histopathology indicated a range of microscopic changes in cats of all groups, with no indication of relationship to or differences between treatments.

Study 2

Nominal dosages were 0, 2, 6 and 10 mg/kg robenacoxib twice daily, respectively, in groups A, B, C and D. Actual daily dosages received by Groups B, C and D were respectively: 4.7 ± 0.53 mg/kg (males) and 4.7 ± 0.54 mg/kg (females) in Group B; 13.3 ± 0.66 mg/kg (males) and 13.2 ± 0.71 mg/kg (females) in Group C, and 21.2 ± 0.77 mg/kg (males) and 21.9 ± 1.02 mg/kg (females) in Group D.

No cat died or became moribund during the study. The physical examinations [comprising assessment of general health, integument and mucous membranes, auscultation of heart and lungs, examination of head (including mouth, eyes and ears) and central nervous system (including reaction to stimuli and measurement of body temperature)] revealed no toxicologically relevant effects in any robenacoxib-treated group, relative to the placebo group. Vomiting was the most commonly reported adverse reaction, but the incidence was similar in all groups. Likewise, soft faeces were reported occasionally with no differences between groups. Although a heart arrhythmia was recorded in a single cat, on day 37, it was transient and not reported on other days.

Body weights and food consumption were recorded on three occasions in the baseline period and on six occasions (once weekly) during treatment. Body weights increased slightly or remained constant throughout the study, with no differences between groups and likewise no differences in food intake (data not shown).

For most haematology variables, there were no statistically significant differences from placebo-treated cats for all robenacoxib-treated groups (selected results shown in Table 4, not all data shown). However, relative to the placebo group, mean cellular haemoglobin concentration was decreased in Groups C and D at day 14 but not at day 35. The changes from baseline at day 14 were slight, comprising +0.22%, −2.98% and −4.02% for Groups A, C and D, respectively.

Table 4. Summary of blood haematology data for cats in study 2; mean (SD), $n = 8$ unless stated

Variable (units)	Day	Group A (placebo)	Group B (robenacoxib 2 mg/kg)	Group C (robenacoxib 6 mg/kg)	Group D (robenacoxib 10 mg/kg)
Erythrocyte count (RBC) (10^{12}/L)	−12	10.2 (1.2)	9.7 (1.0)	10.1 (0.7)	9.5 (2.2)
	−7	9.1 (1.5)	8.7 (0.8)	9.2 (1.0)	8.4 (1.9)
	14	8.5 (0.9) ($n = 7$)	8.2 (1.1)	9.1 (0.8)	8.2 (2.1)
	35	8.3 (1.1)	8.2 (1.4)	8.5 (0.6)	7.5 (1.8)
Haemoglobin concentration (mM)	−12	8.1 (0.6)	7.0 (2.1)	7.9 (0.4)	7.4 (1.4)
	−7	7.3 (0.9)	6.8 (0.6)	7.2 (0.8)	6.5 (1.1)
	14	7.1 (0.6) ($n = 7$)	6.6 (0.7)	7.2 (0.5)	6.5 (1.3)
	35	7.0 (0.6)	6.7 (0.9)	6.8 (0.3)	6.2 (1.2)
Haematocrit (L/L)	−12	0.43 (0.03)	0.40 (0.03)	0.42 (0.01)	0.40 (0.06)
	−7	0.38 (0.04)	0.35 (0.02)	0.37 (0.04)	0.35 (0.06)
	14	0.37 (0.04) ($n = 7$)	0.35 (0.04)	0.39 (0.03)	0.36 (0.06)
	35	0.36 (0.03)	0.35 (0.05)	0.36 (0.01)	0.33 (0.05)
Platelet count (10^9/L)	−12	344.4 (87.9)	305.1 (64.8)	359.1 (64.2)	376.0 (151.1)
	−7	328.5 (120.0)	325.9 (71.7)	342.9 (118.8)	382.8 (120.3)
	14	387.6 (79.7) ($n = 7$)	353.9 (61.7)	419.0 (77.7)	439.6 (125.0)
	35	371.5 (86.7)	379.0 (73.5)	442.5 (71.0)	414.8 (178.3)
Total leucocyte count (10^9/L)	−12	14.7 (4.7)	18.5 (9.5)	14.6 (4.5)	17.2 (3.1)
	−7	16.4 (3.9)	16.5 (6.2)	13.7 (4.2)	17.0 (3.4)
	14	18.3 (4.2) ($n = 7$)	18.0 (7.9)	17.3 (4.8)	18.8 (5.2)
	35	13.8 (3.2)	16.5 (4.0)	13.6 (3.9)	18.7 (6.5)

Differences between placebo and robenacoxib-treated cats were not statistically significant.

For most clinical chemistry variables, there were no significant differences for all robenacoxib-treated groups relative to placebo. Selected results are shown in Table 5 (not all data shown). Although mean AST activity was reduced in Group D cats relative to placebo (Group A), activity of this enzyme was in fact reduced in both Groups (A and D) at day 35, relative to baseline, by 21% in Group A and 29% in Group D. ALT activity was reduced in Groups B and D, compared with Group A. This difference was because of no change in baseline values for Group A cats (+1.8%) and small decreases in Group B (−16%) and D (−26%) animals. In Group B and D cats, GGT activity was increased compared with values in Group A, but the differences were due in part to a decrease from baseline values in Group A at day 14 (−28%), with a small increase in Group B (+28%) at day 14. There was no increase from baseline in any group at day 35.

Serum creatinine and urea concentrations are indirect indicators of integrity of renal function. Compared with Group A, neither variable was significantly changed at days 14 and 35 in the three robenacoxib-treated groups, with one exception; creatinine was increased in Group B cats. However, differences from baseline were slight, increases of 2%, 10%, 3% and 3% occurring in Groups A, B, C and D, respectively, at day 35.

Relative to Group A, calcium concentration increased in Group C cats. However, the difference was attributable to greater decreases in calcium from baseline values in Group A (−4.5% and −2.2% at days 14 and 35) than in Group D (−1.4% and +0.4% at days 14 and 35). Although sodium concentration was increased in Groups C and D relative to Group A, the differences were apparent only at day 14, when increases from baseline were +0.05% (Group A), +1.16% (Group C) and +1.95% (Group D).

Urinalysis revealed a decrease in urine-specific gravity over time in all groups, but there were no differences between groups. There were similarly no group differences in other urine parameters including erythrocytes, leucocytes, epithelial cells, casts, organisms or crystals.

At necropsy, few macroscopic findings were reported and none, with the possible exception of the thymus gland, could be considered treatment related. Small thymuses were noted in individual cats of all groups, and this was reflected in decreased thymus weights. These were significantly reduced in all three groups of robenacoxib-treated cats compared with those in the placebo group (Table 6). However, when two outlier values were excluded from Group A, thymus weight differences in the robenacoxib groups were not significantly different from the placebo group. There were no other significant differences in organ weights. Microscopic examination of the following tissues revealed no treatment-related effects: adrenals, aorta, brain, caecum, colon, duodenum, epididymides, eyes with optic nerves,

Table 5. Summary of serum clinical chemistry data for cats in study 2; mean (SD), $n = 8$ unless stated

Variable (units)	Day	Group A (placebo)	Group B (robenacoxib 2 mg/kg)	Group C (robenacoxib 6 mg/kg)	Group D (robenacoxib 10 mg/kg)
Alanine aminotransferase (IU/L)	−12	99.4 (37.2)	72.5 (29.0)	86.9 (52.5)	64.8 (18.0)
	−7	215.3 (337.3)	68.5 (30.2)	66.9 (28.4)	97.1 (109.6)
	14	153.6 (137.9) ($n = 7$)	56.5 (19.2)*	63.8 (30.0)	45.3 (15.2)*
	35	77.5 (50.0)	82.8 (60.0)	47.9 (13.0)	42.5 (16.5)
Aspartate aminotransferase (IU/L)	−12	24.5 (7.3)	19.5 (5.0)	19.0 (6.5)	17.9 (6.6)
	−7	38.8 (44.7)	20.4 (7.2)	18.8 (8.5)	27.4 (33.1)
	14	29.1 (16.0) ($n = 7$)	22.8 (5.1)	20.3 (6.8)	17.0 (2.8)*
	35	20.4 (6.6)	21.8 (10.3)	12.6 (2.6)	12.8 (3.2)*
Alkaline phosphatase (IU/L)	−12	195.0 (62.2)	153.6 (37.2)	216.9 (95.5)	159.5 (59.3)
	−7	205.0 (61.0)	160.3 (47.1)	222.8 (98.5)	162.6 (51.3)
	14	180.7 (62.2) ($n = 7$)	167.8 (70.0)	187.9 (63.7)	139.4 (38.6)
	35	153.8 (64.4)	132.8 (37.1)	164.6 (61.3)	112.0 (32.2)
Gamma-glumatyltransferase (IU/L)	−12	11.1 (1.9)	9.4 (2.5)	9.5 (2.2)	8.9 (3.1)
	−7	6.3 (1.4)	6.3 (1.3)	5.6 (1.5)	6.6 (1.3)
	14	6.1 (2.0) ($n = 7$)	9.8 (2.0)**	6.3 (1.4)	8.6 (4.2)*
	35	6.6 (1.8)	7.4 (2.4)**	6.3 (1.7)	7.3 (1.8)*
Creatinine (μM)	−12	132.3 (26.1)	130.5 (12.7)	134.5 (13.7)	133.6 (21.4)
	−7	113.8 (18.7)	122.4 (16.1)	118.8 (8.4)	123.4 (18.2)
	14	113.9 (17.l) ($n = 7$)	129.4 (13.3)*	119.3 (15.1)	119.4 (16.9)
	35	124.8 (23.5)	137.6 (12.6)*	130.0 (11.3)	132.3 (19.6)
Blood urea nitrogen (mM)	−12	6.5 (1.8)	6.8 (1.4)	6.4 (1.2)	6.7 (1.3)
	−7	6.3 (1.4)	7.1 (1.3)	7.2 (0.9)	6.7 (1.3)
	14	8.4 (1.0) ($n = 7$)	8.6 (1.5)	8.5 (1.3)	9.1 (1.2)
	35	9.0 (1.1)	8.9 (0.8)	10.1 (0.8)	9.6 (1.1)
Total protein (g/L)	−12	64.4 (1.6)	65.4 (4.2)	65.3 (2.6)	64.8 (5.1)
	−7	61.5 (2.4)	60.7 (2.5)	61.4 (2.4)	61.3 (4.2)
	14	60.9 (1.8) ($n = 7$)	61.4 (2.6)	61.0 (2.9)	60.9 (4.8)
	35	58.3 (3.0)	62.1 (2.0)	61.2 (2.5)	59.5 (5.3)

Statistical differences between placebo and robenacoxib-treated cats: *$P < 0.05$; **$P < 0.01$.

Table 6. Summary of body (kg) and organ (g) weights in cats in study 2; mean (SD), n = 8 unless stated

Organ	Group A (placebo)	Group B (robenacoxib 2 mg/kg)	Group C (robenacoxib 6 mg/kg)	Group D (robenacoxib 10 mg/kg)
Final bodyweight	3.4 (1.0)	3.4 (0.8)	3.6 (0.6)	3.2 (0.7)
Heart	14.0 (4.5)	12.8 (3.7)	17.2 (8.6)	14.4 (4.4)
Kidneys	21.2 (8.5)	22.0 (8.7)	21.5 (5.8)	20.7 (10.3)
Liver	99.5 (32.3)	96.6 (30.3)	97.2 (18.7)	96.3 (29.8)
Thymus	2.7 (1.9)	1.5 (0.5)*	1.3 (0.5)*	1.3 (0.5)*
Thymus†	1.8 (0.9) (n = 6)	1.5 (0.5)	1.3 (0.5)	1.3 (0.5)
Spleen	21.1 (8.9)	19.9 (12.4)	21.1 (8.2)	18.1 (10.3)
Testes (n = 4)	2.5 (0.5)	2.7 (0.3)	2.7 (0.3)	3.1 (1.2)
Ovaries (n = 4)	0.36 (0.1)	0.36 (0.05)	0.40 (0.05)	0.35 (0.03)
Uterus (n = 4)	3.2 (2.1)	2.8 (0.7)	3.1 (0.4)	2.7 (1.0)
Thyroid	0.26 (0.1)	0.35 (0.3)	0.25 (0.06)	0.22 (0.09) (n = 7)
Adrenals	0.42 (0.1)	0.42 (0.1)	0.35 (0.07)	0.41 (0.2)
Pituitary	0.040 (0.001)	0.032 (0.01)	0.035 (0.01)	0.030 (0.01)
Brain	28.1 (2.2)	26.5 (2.7)	27.0 (2.2)	27.4 (1.7)

Statistical differences between placebo and robenacoxib-treated cats: *P < 0.01. †Excluding animal nos. 3 and 4 in Group A only as outliers.

femur (distal with articular surface and bone marrow), gall bladder, heart, ileum, jejunum, kidneys, lacrimal glands, larynx, liver, lung, lymph nodes (cervical, mesenteric and mediastinal), mammary area, oesophagus, ovaries, oviducts, pancreas, peripheral nerves, pituitary, prostate, rectum, salivary glands, skeletal muscle, skin, spinal cord, spleen, sternum (with bone marrow), stomach, synovial membrane (knee joint), testes, thymus, thyroid (with parathyroid), tongue, trachea, ureters, urinary bladder, uterus (with cervix) and vagina.

Blood robenacoxib concentrations

Blood samples collected on day 35 approximately 12 h after dosing in study 2 were analysed for blood robenacoxib. No drug was detected in any of the eight placebo-treated cats. Low concentrations of robenacoxib, ≥3 ng/mL, were detected in two of eight cats receiving 2 mg/kg (3 and 3.1 ng/mL), four of eight cats with 6 mg/kg (3, 3.2, 4.6 and 5.2 ng/mL) and eight of eight cats with 10 mg/kg (3.9, 4.6, 4.9, 5, 7.1, 9.6, 10.6 and 11.6 ng/mL), indicating rapid clearance of the drug from blood.

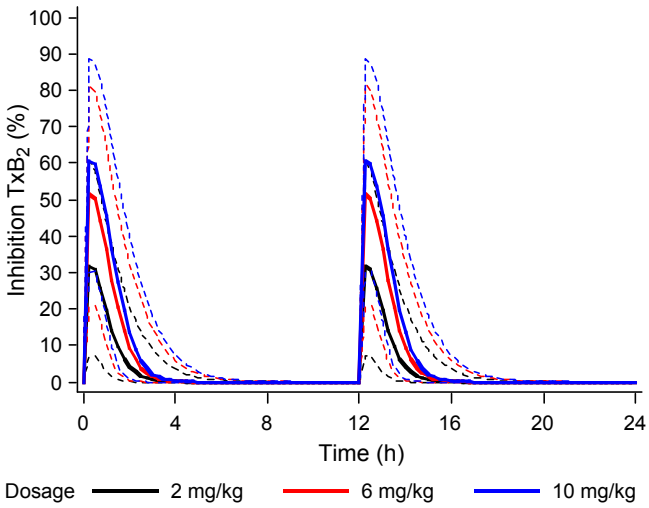

Fig. 1. Simulated inhibition of serum TxB_2, as an index of cyclooxygenase-1 inhibition, after oral administration to fasted cats of robenacoxib at three dosages twice daily (study 2). Data are the median (full line) and 90% tolerance intervals (dotted lines).

PK–PD simulations

Median and 90% tolerance intervals for simulations in 100 cats for inhibition of COX-1 (TxB_2 used as surrogate) and COX-2 (PGE_2 as surrogate) are illustrated in Figs 1 & 2. For safety assessments, the median and upper limits of the 90% tolerance interval are considered. At 2 mg/kg, the median maximum inhibition of COX-1 was 30.6% and inhibition exceeded 10% for 0.8 h (Fig. 1). In contrast, at the same dosage, the median maximum inhibition of COX-2 was 97.8% and inhibition exceeded 50% for 2.3 h (Fig. 2). More prolonged inhibition of COX-1 and COX-2 occurred at higher dosages but, even at the 10 mg/kg dosage, median COX-1 inhibition did not exceed 50% for more than 0.5 h and the median COX-2 inhibition exceeded 50% for only 2.9 h. For the upper limit of the 90% tolerance interval at 10 mg/kg, the peak inhibition of COX-1 was 93.3%, 50% inhibition persisted for 1.5 h, and 10% inhibition persisted for 3 h. For the upper limit of the 90% tolerance interval at 10 mg/kg, the peak inhibition for COX-2 was 100%, 50% inhibition persisted for 4.4 h, and 10% inhibition persisted for 6.1 h.

DISCUSSION

Principal findings and context to literature

The primary objective of this study was to evaluate the safety of robenacoxib tablets in cats with repeated oral administration. It was concluded that administration of robenacoxib was well

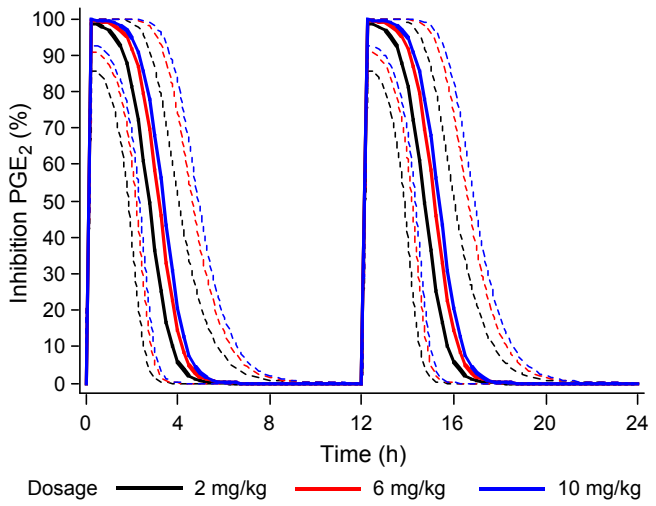

Fig. 2. Simulated inhibition of plasma prostaglandin E_2, as an index of cyclooxygenase-2 inhibition, after oral administration to fasted cats of robenacoxib at three dosages twice daily (study 2). Data are the median (full line) and 90% tolerance intervals (dotted lines).

tolerated at 5–10 mg/kg once daily for up to 1 month (study 1) and at 2–10 mg/kg twice daily for up to 6 weeks (study 2), with no biologically relevant treatment-related toxicity. This conclusion was based on general observations of health, food and water consumption, body weight changes, haematological, clinical chemistry and urine analyses, and by *post mortem* organ weight, gross pathology and histopathology assessments. Although statistically significant differences from placebo were observed for some haematological and clinical chemistry variables, it was judged that no biologically relevant effects of robenacoxib were present for the following reasons: (i) some changes were too small numerically to signify toxicity; (ii) some significant differences from placebo were because of a change with time in placebo values, such that changes from baseline (predosing) values occurred with placebo treatment but not in robenacoxib-treated cats; (iii) some plasma enzyme activity changes in robenacoxib-treated cats were because of decreases relative to placebo treatment, when it is increased activity which signifies potential toxicity; (iv) some differences from placebo treatment were not dose-related but occurred, for example, in low and/or medium robenacoxib groups but not in cats receiving the high dosage of robenacoxib; and (v) some differences from placebo occurred in only one of the two studies. For example, some haematological and clinical chemistry variable differences between placebo and robenacoxib-treated groups differed between study 1 and study 2.

The principal targets for toxicity of nonselective NSAIDs are damage to the gastrointestinal tract, kidney and liver, and inhibition of blood clotting (Warner *et al.*, 1999; Flower, 2003). No evidence of toxicity of robenacoxib to any of these systems was detected in the cats in either study 1 or 2. Regarding the gastrointestinal tract, no changes in serum total protein or albumin concentrations, which would indicate protein-losing enteropathy, were detected, and no gross or histopathological signs of damage or ulceration were observed. In addition, no gross or histopathological changes in the kidney or liver, and no changes in biochemical indicators of deterioration of kidney function (serum creatinine or urea concentration) or liver damage (serum transferase activities) were detected. Finally, at no dosage did robenacoxib affect the activated partial thromboplastin time. Similar results were reported recently with robenacoxib in dogs (King *et al.*, 2011).

It is recognised that the methods used for testing robenacoxib safety were not in all cases the most sensitive. For example, we did not assess, during the in-life phase, the appearance of the stomach via gastroscopy or check for the presence of occult faecal blood (only gross appearance of the faeces was checked). In addition, reliance was placed on plasma creatinine concentration as an approximate and indirect measure of glomerular filtration rate. Nevertheless, we conclude that the methods were sufficiently sensitive and robust to conclude that robenacoxib produced no biologically relevant toxicity, even at the highest dosage of 20 mg/kg daily for 42 days.

Robenacoxib tablets are registered in the European Union for acute musculoskeletal disorders in cats at a dosage of 1–2.4 mg/kg for up to 6 days. Therefore, the upper dosages tested in this study represent 4–10 (28 days, study 1) and 8.3–20 (42 days, study 2) multiples of the clinically recommended daily dosage. The results of this study indicate that the safety index of robenacoxib is high in cats, and to our knowledge is higher than published for any other NSAID in this species (Lascelles *et al.*, 1995, 2007; Runk *et al.*, 1999; Papich, 2008).

Cats were dosed with robenacoxib tablets approximately 1 h before feeding in study 2. In study 1, cats were fed *ad libitum,* and therefore it is unlikely that a large amount of food was present in the stomach at the time of each dosing. The oral bioavailability of robenacoxib from tablets is reduced in cats when given with the entire daily ration, but not when co-administered with one third of the daily ration (J.N. King, M. Jung, M.P. Maurer, V.B. Schmid, W. Seewald & P. Lees, In preparation). In addition, the T_{max} of robenacoxib in blood is 0.5 h after oral administration in fasted cats (J.N. King, M. Jung, M.P. Maurer, V.B. Schmid, W. Seewald & P. Lees, In preparation). Therefore, it is concluded that oral bioavailability was probably optimal in both studies, and consistent with the label recommendations in the European Union, i.e., to administer Onsior® (Novartis Animal Health) tablets to cats either without food or with a small quantity of food.

Different tablet formulations were used in studies 1 and 2, namely nonflavoured lactose tablets in study 1 and the flavoured tablets presently marketed (Onsior®; Novartis Animal Health) in study 2. However, this should have had no impact on the conclusions of the studies as the two formulations have been shown to be bioequivalent for both C_{max} and AUC (Novartis Animal Health data on file).

PK–PD simulations

It has been concluded in humans that inhibition of COX-1 makes the major and possibly sole contribution to the gastrointestinal toxicity of nonselective NSAIDs (Warner *et al.*, 1999), although

Wallace *et al.* (2000) concluded in rats that NSAID-induced gastrointestinal damage required simultaneous inhibition of both COX-1 and COX-2. The exact extent of inhibition of COX-1 needed to induce damage to the gastrointestinal tract is not known (Warner *et al.*, 1999), although it is logical that damage will be a function of the duration as well as magnitude of inhibition of COX-1. To explore the extent and duration of COX isoforms inhibition by robenacoxib in cats, simulations of the predicted inhibition of COX-1 and COX-2 in the central compartment with the dosages of robenacoxib tested in this study were created. All of these dosages had produced no detectable toxicity to the gastrointestinal tract. Similar simulations were reported recently for robenacoxib in dogs (King *et al.*, 2011). Even though robenacoxib is a highly selective inhibitor of COX-2 in cats, with a potency ratio for 50% inhibition of COX-1:COX-2 exceeding 500:1 (Giraudel *et al.*, 2009a), transient inhibition of COX-1 was predicted at early time points after dosing with the high dosages of robenacoxib used in this study (Fig. 1). In all cats, there was greater inhibition of COX-2 simultaneously with the slight inhibition of COX-1 (Fig. 2). As no biologically relevant toxicity was detected with any dosage of robenacoxib, it is concluded that 50% inhibition of COX-1 for 1.5 h, or 10% for 3 h (the upper limits of the 90% tolerance interval at the highest robenacoxib dosage tested of 10 mg/kg) with maximal inhibition and somewhat longer inhibition of COX-2 with robenacoxib twice daily did not affect the cats adversely.

CONCLUSIONS

Robenacoxib tablets had an excellent safety profile in young healthy domestic short-haired cats, when administered at daily dosages up to 10 mg/kg for 28 days and up to 20 mg/kg for 42 days. The absence of toxicity occurred even though the greatest PD effect of robenacoxib was predicted to be 50% inhibition of COX-1 for 1.5 h, or 10% inhibition for 3 h, together with marked inhibition of COX-2. The results of this feline study support the conclusion, as previously reported for rats and dogs (King *et al.*, 2009, 2011), that the excellent safety profile of robenacoxib may be because of a combination of PD (high selectivity for COX-2) and PK (rapid clearance from the central compartment with longer residence times at sites of inflammation) properties. It should be noted that the safety studies reported in this paper were conducted in healthy young domestic short-haired cats. The same conclusions might not apply to other breeds, or to cats with pre-existing damage to the gastrointestinal tract, kidney or liver. Results of field studies in cats with naturally occurring diseases are required to complete the safety profiling of robenacoxib in cats.

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