

Effects of route of administration and feeding schedule on pharmacokinetics of robenacoxib in cats

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Objective—To establish pharmacokinetics of robenacoxib after administration to cats via the IV, SC, and oral routes.

Animals—24 cats.

Procedures—In a crossover design, robenacoxib was administered IV, SC, and orally (experiment 1) and orally (experiment 2) to cats with different feeding regimens. Blood robenacoxib concentrations were assayed, with a lower limit of quantification of 3 ng/mL.

Results—In experiment 1, geometric mean pharmacokinetic values after IV administration of robenacoxib were as follows: blood clearance, 0.44 L/kg/h; plasma clearance, 0.29 L/kg/h; elimination half-life, 1.49 hours; and volume of distribution at steady state (determined from estimated plasma concentrations), 0.13 L/kg. Mean bioavailability was 69% and median time to maximum concentration (C_{max}) was 1 hour for cats after SC administration of robenacoxib, whereas mean bioavailability was 49% and 10% and median time to C_{max} was 1 hour and 30 minutes after oral administration to cats after food withholding and after cats were fed their entire ration, respectively. In experiment 2, geometric mean C_{max} was 1,159, 1,201, and 692 ng/mL and area under the curve from 0 to infinity was 1,337, 1,383, and 1,069 ng × h/mL following oral administration to cats after food withholding, cats fed one-third of the daily ration, and cats fed the entire daily ration, respectively.

Conclusions and Clinical Relevance—For treatment of acute conditions in cats, it is recommended to administer robenacoxib by IV or SC injection, orally after food withholding, or orally with a small amount of food to obtain optimal bioavailability and C_{max}. (*Am J Vet Res* 2013;74:465–472)

Robenacoxib is an NSAID used for the management of pain and inflammation in cats and dogs. In the United States, tablets of robenacoxib are the only approved formulation for cats. Analgesic, anti-inflammatory, and antipyretic properties of robenacoxib have been determined in cats with kaolin-induced acute paw inflammation and acute musculoskeletal disorders and in cats undergoing surgery.^{1–3} The safety after oral administration of robenacoxib to healthy cats has been reported, with administration of dosages up to 20 mg/kg/d for 42 days tolerated well.⁴ This compares with la-

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ABBREVIATIONS

| | |
|----------------------|--|
| AUC _{0–inf} | Area under the blood concentration–time curve from time 0 to infinity |
| AUC _{0–t} | Area under the blood concentration–time curve from time 0 to the last measurable concentration |
| CI | Confidence interval |
| C _{max} | Maximum concentration |
| COX | Cyclooxygenase |
| CV | Coefficient of variation |
| IC ₅₀ | Concentration providing 50% of maximum inhibition |
| I _{max} | Maximum inhibition |
| MRT | Mean residence time |
| PI | Predictive interval |
| T _{max} | Time of maximum concentration |
| Vd _{area} | Volume of distribution during the elimination phase |
| Vd _{ss} | Volume of distribution at steady state |

beled robenacoxib doses of 2 mg/kg by SC injection and 1 to 2.4 mg/kg via oral administration. Pharmacokinetics of robenacoxib after IV, oral, and SC administration to cats have also been reported.^{1,5}

The objective of the study reported here was to provide additional data on robenacoxib by further defining its pharmacokinetics in healthy cats after oral and parenteral administration. Specific objectives were to determine pharmacokinetics of robenacoxib after IV administration, establish pharmacokinetic profiles after oral and SC administration, determine the impact of feeding regimen and food withholding on pharmacokinetics of robenacoxib administered orally, and estimate via pharmacokinetic-pharmacodynamic simulations the clinical implications of the impact of feeding.

Materials and Methods

Animals—European Shorthair cats were used in 2 experiments. In experiment 1, 12 cats (6 males and 6 females) weighing 2.5 to 5.1 kg and 11 months old at the start of the experiment were used. In experiment 2, 12 cats (6 males and 6 females) weighing 3.2 to 4.4 kg and 2 to 4 years old at the start of the experiment were used. Cats were allowed to acclimate for 8 days prior to the first administration of robenacoxib. The cats were housed in groups to facilitate social interaction but were kept in separate cages for 8 (experiment 1) or 10 (experiment 2) hours after robenacoxib administration. The daily light cycle was 14 hours of light and 10 hours of darkness. The daily food ration comprised a dried pelleted food^a supplied in the morning once daily. Drinking water was available ad libitum. All cats remained in good health throughout the study, as indicated on the basis of results of physical examinations and hematologic and blood biochemical analyses.

The study was performed in 2 parts (experiments) in compliance with good laboratory practice procedures and guidelines on bioanalytics and pharmacokinetic and bioequivalence studies.⁶⁻⁸ The protocols were approved via internal reviews by personnel at Novartis Animal Health Inc with consideration for ethical, scientific, and welfare aspects.

Study design—Robenacoxib was administered in a 4-phase (experiment 1) or 3-phase (experiment 2) crossover Latin square design. Cats were allocated to treatment groups by means of a computerized random number procedure.^b In experiment 1, robenacoxib was administered IV and SC to cats (3 cats/group) fed their entire daily ration, orally to cats fed the entire ration, and orally to cats from which food was withheld for at least 12 hours. In experiment 2, robenacoxib was administered orally to cats (4 cats/group) fed one-third of the daily ration, fed the entire daily ration, or from which food was withheld for at least 12 hours. There was a 1-week washout interval between subsequent treatments. Time of drug administration was designated as time 0.

In experiment 1, on days on which robenacoxib was administered, the feeding schedule involved provision of the entire daily ration of food in the morning within 30 minutes before drug administration (cats receiving IV and SC injections and cats receiving oral administration after being fed the entire daily ration) or approximately 2 hours after drug administration (cats receiving oral administration after food was withheld). For IV administration, robenacoxib (2 mg/kg)

was injected into a cephalic vein. A water-based 0.4% (wt/vol) solution of robenacoxib^c containing propylene glycol (15% [wt/vol]) and tromethamine as excipients was used for IV administration. For SC administration, robenacoxib (2 mg/kg) was injected in the tissues at the nape of the neck. An aqueous robenacoxib solution^d (20 mg/mL) was used for SC administration. For oral administration, each cat received a single tablet^e that contained 6 mg of robenacoxib and a flavoring agent.

In experiment 2, the 3 treatments (4 cats [2 males and 2 females]/group) were oral administration of robenacoxib to cats fed the entire daily ration 30 minutes to 1 hour before drug administration, cats fed one-third of the daily ration at the time of drug administration and then fed the remaining two-thirds of the daily ration 3 hours after drug administration, and cats from which food was withheld before drug administration and then were fed the entire daily ration 3 hours after drug administration. Each cat received a single tablet^e containing 6 mg of robenacoxib and a flavoring agent.

In both experiments, robenacoxib tablets were administered to cats from which food was withheld by placing a tablet in the caudal aspect of the pharynx of each cat. In experiment 2, but not experiment 1, a dosing syringe then was used to administer a small amount of water to each cat.

Blood sample collection—Blood samples (1.2 mL/sample) for measurement of blood concentrations of robenacoxib were collected from a cephalic or jugular vein into tubes that contained EDTA as an anticoagulant.^f In experiment 1, a blood sample was collected at 3 minutes (IV treatment only). Blood samples were collected from all cats at 15 and 30 minutes and 1, 2, 3, 4, 5, 6, and 8 hours. In experiment 2, blood samples were collected at 30 minutes and 1, 2, 3, 4.5, 6, 8, and 10 hours. Samples were stored at -16°C or colder prior to analysis.

Analysis of robenacoxib concentration in blood—Concentrations of robenacoxib in blood were determined via a previously validated analytic method.⁹ An initial analysis was performed via high-performance liquid chromatography with UV detection for the concentration range of 500 to 20,000 ng/mL. When required, a subsequent analysis by liquid chromatography with mass spectrometry for the range of 3 to 100 ng/mL was performed. The lower limitation of quantification in cat blood was 3 ng/mL. Quality-control spiked matrix samples were included with every sequence of unknown samples. For 6 samples on each of 5 sequences (30 analyses), the maximum deviations were -9.2% and 14.2% for the UV method. For 33 samples in 4 sequences, maximum deviations for the mass spectrometry method were -13.9% and 12.7% . Robenacoxib concentrations were stable in frozen blood for at least 156 days.

Robenacoxib is extensively ($> 98\%$) bound to plasma proteins, and its pharmacological activity is related to the free (unbound) drug. Total robenacoxib concentrations in blood were measured because the binding of robenacoxib to plasma proteins is linear in cats and therefore the free concentration is proportional to the total concentration.⁹ In addition, measurement of the amount of free drug with a lower limitation of quantifi-

cation of 3 ng/mL for the analytic method would have allowed us to determine free robenacoxib concentrations in blood for only 1 to 2 hours after drug administration at the doses used.

Pharmacokinetic analyses—Blood concentration–time profiles were processed with a computer program⁸ to generate standard pharmacokinetic variables that included C_{max}, T_{max}, area under the blood concentration–time curve, AUC_{0–t}, AUC_{0–inf}, area under the first moment curve from 0 to infinity, MRT (area under the first moment curve from 0 to infinity/AUC_{0–inf}), terminal half-life during the elimination phase (determined by linear regression of the logarithmic concentration versus time curve during the elimination phase, with the best model determined by the least squares method), blood clearance (dose/AUC_{0–inf}), and bioavailability (AUC_{0–inf} after SC or oral administration/AUC_{0–inf} after IV administration, with dose-normalized data). In whole blood, robenacoxib resides almost exclusively in the plasma because it is highly (> 98%) protein bound, with little penetration into blood cells.⁹ Therefore, in addition to the clearance from blood, the clearance of robenacoxib from plasma was calculated as blood clearance multiplied by the blood-to-plasma concentration ratio.¹⁰ The blood-to-plasma concentration ratio for robenacoxib was previously found to be 0.65 in healthy cats,⁹ and this correlated well with the mean Hct of 0.35 for the cats of the present study.

Apparent volumes of distribution were determined with measured blood concentrations and estimated plasma concentrations. The Vd_{area} was calculated as clearance of robenacoxib from blood × half-life/ln 2 = dose/(AUC_{0–inf} × k_e), where k_e is the elimination-phase constant. The Vd_{ss} was calculated as clearance of robenacoxib from blood × MRT.

Statistical analysis—Pharmacokinetic variables were expressed as the geometric mean and SD, except for T_{max}, which was expressed as the median. Dose-dependent pharmacokinetic variables (concentration at time 0, C_{max}, AUC_{0–t}, AUC_{0–inf}, and bioavailability) were normalized with respect to dose.

Data for all variables, except for T_{max}, were evaluated with the Shapiro-Wilk test to determine whether there was a normal distribution, and statistical analyses were conducted on original or logarithmically transformed data, as appropriate. Differences between groups were tested via an ANOVA, unless the data were not normally distributed, in which case the Mann-Whitney U test was used. Several covariates were included in the ANOVA models, which included group (route of administration in experiment 1 and feeding regimen in experiments 1 and 2), animal, sex, phase (1 to 4 in experiment 1 and 1 to 3 in experiment 2), and sequence of treatments.

The effect of feeding after oral administration was evaluated via an ANOVA with bioequivalence analysis, with food withholding as the reference feeding regimen.⁷ The AUC_{0–inf} was used as the primary variable, with AUC_{0–t} and C_{max} as secondary variables. Bioequivalence for AUC values was assessed as whether the calculated 90% CI for the relative bioavailability was within the predefined acceptance interval of 0.80

to 1.25. For C_{max}, the default acceptance interval was 0.70 to 1.43 because C_{max} was based on a single point estimate.

Statistical software^h was used for all analyses. Two-tailed values of P < 0.05 were considered significant.

Pharmacokinetic-pharmacodynamic simulations—Pharmacokinetic-pharmacodynamic simulations were performed with methods described previously⁴; simulations were performed with pharmacokinetic data from the present study and pharmacodynamic data generated in a previous study.¹¹ Briefly, a 1-compartment pharmacokinetic model was fitted to each of the blood concentration–time profiles as follows:

$$\text{Robenacoxib concentration in blood} = (\text{FD}/V) \times K_{10} \times t \times \exp(-K_{10} \times t)$$

where FD is the absorbed dose, V is the volume of distribution, K₁₀ is the rate constant for elimination, t is the time after drug administration, and exp is the exponential. It was assumed that the rate constant for absorption was equal to K₁₀, which was appropriate for most of the profiles.

Fitting parameters involved optimizing a nonlinear function, which was conducted iteratively. Only good model fits, as indicated when the slope was significantly different from 0, were used.

The standard sigmoidal (Hill) model for pharmacodynamic data was used to establish predicted profiles of inhibition of COX-1 and COX-2 as follows:

$$\text{Percentage inhibition} = (\text{Imax} \times C^n) / (\text{IC}_{50}^n + C^n)$$

where C is the total concentration of robenacoxib in the blood and n is the slope parameter. Values for n and IC₅₀ were obtained from geometric mean and 95% PIs reported elsewhere.¹¹ Geometric mean ± geometric SD of n and IC₅₀ were 0.79 ± 1.48 and 7,298 ± 2.17 ng/mL, respectively, for inhibition of COX-1 and 0.89 ± 1.56 and

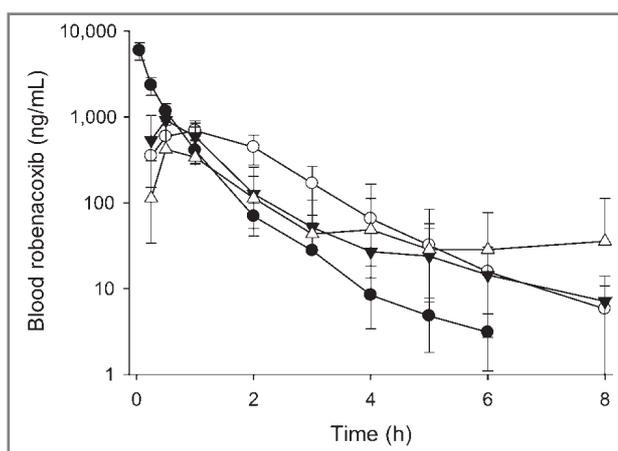


Figure 1—Semilogarithmic plot of mean ± SD blood concentration–time profiles after administration of a single dose of robenacoxib to 12 cats. Treatments were IV injection (2 mg/kg) after cats were fed the entire daily ration (black circles), SC injection (2 mg/kg) after cats were fed the entire daily ration (white circles), oral administration of a 6-mg tablet after cats were fed the entire daily ration (white triangles), and oral administration of a 6-mg tablet after food was withheld from the cats (inverted black triangles). All profiles are normalized to a dose of 1 mg/kg.

Table 1—Pharmacokinetic variables for robenacoxib administered IV, SC, and orally to 12 cats after they were fed their entire daily ration and orally to those same 12 cats after food was withheld.

| Variable | IV | | SC | | Oral | | | |
|--|---------------------|--------|---------------------|--------|---------------------|--------|---------------------|--------|
| | Geometric mean ± SD | CV (%) | Geometric mean ± SD | CV (%) | Entire daily ration | | Food withheld | |
| | | | | | Geometric mean ± SD | CV (%) | Geometric mean ± SD | CV (%) |
| C _{max} or C ₀ (ng/mL)*† | 7,365 ± 1,909 | 25 | 732 ± 158 | 21 | 125 ± 612 | 116 | 773 ± 502 | 52 |
| AUC _{0-t} (ng × h/mL)† | 2,276 ± 488 | 21 | 1,554 ± 263 | 17 | 207 ± 683 | 91 | 1,090 ± 437 | 37 |
| AUC _{0-inf} (ng × h/mL)† | 2,282 ± 489 | 21 | 1,564 ± 264 | 17 | 225 ± 686‡ | 90 | 1,122 ± 426 | 35 |
| MRT (h) | 0.44 ± 0.11 | 25 | 1.67 ± 0.45 | 26 | NC | NC | 1.48 ± 1.11 | 65 |
| Terminal half-life (h) | 1.49 ± 0.43 | 28 | 1.11 ± 0.14 | 13 | NC | NC | 1.71 ± 0.65 | 36 |
| Clearance (L/kg/h)§ | | | | | | | | |
| Blood | 0.44 ± 0.09 | 20 | — | — | — | — | — | — |
| Plasma | 0.29 ± 0.06 | 20 | — | — | — | — | — | — |
| V _{d_{area}} (L/kg)§ | | | | | | | | |
| Blood | 0.94 ± 0.26 | 27 | — | — | — | — | — | — |
| Plasma | 0.61 ± 0.17 | 27 | — | — | — | — | — | — |
| V _{d_{ss}} (L/kg)§ | | | | | | | | |
| Blood | 0.19 ± 0.06 | 31 | — | — | — | — | — | — |
| Plasma | 0.13 ± 0.04 | 31 | — | — | — | — | — | — |
| Bioavailability (%)† | — | — | 0.69 ± 0.09 | 13 | 0.10 ± 0.27 | 88 | 0.49 ± 0.16 | 31 |

The dose of robenacoxib administered was 2 mg/kg for IV and SC administrations and 6 mg/cat for oral administration; time of administration of robenacoxib was designated as time 0. Values were derived from robenacoxib concentrations in blood, unless otherwise indicated.

*For IV administration, concentration at time 0 (C₀) is reported instead of C_{max}; the C₀ is calculated by log-linear extrapolation to time 0 by use of the first 2 data points. †Normalized on the basis of a dose of 1 mg/kg for all cats. ‡For 3 of 12 cats, area under the blood concentration–time curve from the last measurable concentration to infinity could not be determined; therefore, AUC_{0-t} = AUC_{0-inf}. §Clearance and volume of distribution were determined from measured concentrations in blood and estimated concentrations in plasma via a blood-to-plasma concentration ratio of 0.65.

— = Not applicable. NC = Not calculated.

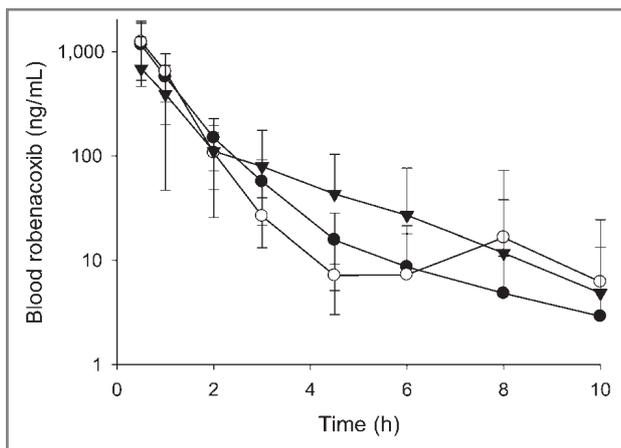


Figure 2—Semilogarithmic plot of group mean ± SD blood concentration–time profiles after oral administration of a single dose of robenacoxib (6-mg tablet) to 12 cats when food was withheld (black circles) or when cats were fed one-third of the daily ration (white circles) or the entire daily ration (inverted black triangles). All profiles are normalized to a dose of 1 mg/kg.

21.0 ± 2.49 ng/mL, respectively, for inhibition of COX-2.

Based on 10,000 simulations, values for the log₁₀ volume of distribution, log₁₀ AUC, and slope and log₁₀ IC₅₀ for COX-1 and COX-2 were selected randomly from the underlying distributions (taking into account the correlations). Blood concentrations of robenacoxib and the corresponding magnitude of inhibition of COX-1 and COX-2 were calculated via the underlying models. Medians and 90% PIs were calculated and plotted against time. All calculations were performed with statistical software.^h

Results

Experiment 1—The administered dose was the same as the calculated dose (2 mg/kg) for cats receiving robenacoxib IV or SC. For cats receiving robenacoxib

Table 2—Blood pharmacokinetic variables after oral administration of robenacoxib (6-mg tablet) to 12 cats when food was withheld or when cats were fed one-third of the daily ration or the entire daily ration.

| Variable | Feeding regimen | Geometric mean | CV (%) |
|-----------------------------------|------------------|-----------------|--------|
| C _{max} (ng/mL)* | Food withheld | 1,158.9 ± 600.0 | 51.8 |
| | One-third ration | 1,200.9 ± 775.2 | 64.6 |
| | Entire ration | 691.8 ± 580.2 | 83.9 |
| AUC _{0-t} (ng × h/mL)* | Food withheld | 1,310 ± 436 | 33.3 |
| | One-third ration | 1,355 ± 420 | 31.0 |
| | Entire ration | 1,030 ± 262 | 25.4 |
| AUC _{0-inf} (ng × h/mL)* | Food withheld | 1,337 ± 469 | 35.1 |
| | One-third ration | 1,383 ± 386 | 27.9 |
| | Entire ration | 1,069 ± 250 | 23.4 |
| MRT (h) | Food withheld | 1.44 ± 0.72 | 50.2 |
| | One-third ration | 1.21 ± 0.75 | 62.2 |
| | Entire ration | 1.74 ± 1.55 | 89.3 |
| Terminal half-life (h) | Food withheld | 1.86 ± 1.70 | 91.1 |
| | One-third ration | 1.52 ± 1.05 | 68.9 |
| | Entire ration | 1.65 ± 1.52 | 92.1 |

Geometric mean, SD, and CV values were calculated with logarithmically transformed values and then were back transformed.

*Normalized on the basis of a dose of 1 mg/kg for all cats.

orally, the mean administered dose was 1.75 mg/kg (range, 1.21 to 2.22 mg/kg) for the entire ration treatment and 1.76 mg/kg (range, 1.18 to 2.34 mg/kg) for the food withheld treatment.

Mean blood concentration–time profiles for the 4 dosing regimens were plotted (Figure 1). Mean robenacoxib concentrations for SC administration and oral administration when food was withheld and when cats were fed the entire ration were higher, compared with concentrations after IV administration, at 2 hours and all subsequent sample collection times. Robenacoxib concentration–time profiles in cats receiving IV and SC injections had only small interanimal variations in elimination (IV and SC administration) and absorption (SC administration) profiles.

Table 3—Bioequivalence of blood pharmacokinetic variables after oral administration of robenacoxib (6-mg tablet) to 12 cats when food was withheld or when cats were fed one-third of the daily ration or the entire daily ration.

| Variable | Feeding regimen | P value† | Relative bioavailability (%)* | | |
|------------------------|------------------|----------|-------------------------------|------|------------|
| | | | Estimate | SEM | 90% CI |
| C _{max} ‡ | One-third ration | 0.890 | 103.6 | 27.0 | 66.3–162.0 |
| | Entire ration | 0.060 | 59.7 | 15.5 | 38.2–93.3 |
| AUC _{0–t} ‡ | One-third ration | 0.710 | 103.4 | 9.1 | 88.9–120.3 |
| | Entire ration | 0.012 | 78.6 | 6.9 | 67.6–91.5 |
| AUC _{0–inf} ‡ | One-third ration | 0.670 | 103.5 | 8.2 | 90.4–118.5 |
| | Entire ration | 0.010 | 80.0 | 6.3 | 69.9–91.6 |

*Compared with values obtained when food was withheld from the cats. †Compared with values obtained when food was withheld from the cats; values are considered significant at $P < 0.05$. ‡Normalized on the basis of a dose of 1 mg/kg for all cats.

When cats received robenacoxib orally and were fed the entire ration, concentrations remained low throughout the 8-hour sampling period in 4 cats. In 3 cats, C_{max} was relatively delayed, with T_{max} at 4, 5, or 8 hours, respectively; in 5 cats, T_{max} was at 30 minutes or 1 hour.

Pharmacokinetic variables were summarized (Table 1). Interanimal variation after IV and SC administration was relatively small, as indicated by ranges of CVs of 20% to 31% after IV administration and 13% to 26% after SC administration. When cats received robenacoxib orally, there was greater variation when food was withheld (CV range, 31% to 65%), and high variability (CV range, 88% to 116%) was apparent when cats were fed the entire ration.

After IV administration, clearance of robenacoxib from the blood was 0.44 L/kg/h, clearance from plasma was 0.29 L/kg/h, and the terminal half-life was 1.49 hours. The V_{d_{ss}} was 0.19 or 0.13 L/kg when calculated with the concentration in blood or plasma, respectively. The V_{d_{area}} was higher (0.94 or 0.61 L/kg) when calculated with the concentrations in blood or plasma, respectively. After SC administration, median T_{max} was short (1 hour; range, 1 to 2 hours) and bioavailability was 69%. The MRT was longer after SC administration than after IV administration.

For cats receiving robenacoxib orally, bioavailability was 49% and median T_{max} was short (30 minutes; range, 15 minutes to 1 hour) when food was withheld. The MRT was longer when cats received robenacoxib orally after food was withheld than after IV administration. When cats were fed the entire ration and received robenacoxib orally, there was high interanimal variation in blood concentration–time profiles. The median T_{max} was 1 hour (range, 15 minutes to 8 hours) when cats were fed the entire ration and received robenacoxib orally. There were no significant differences between females and males for any pharmacokinetic variable.

Experiment 2—The mean dose of robenacoxib administered was 1.66 mg/kg (range, 1.50 to 1.94 mg/kg). Mean concentrations of robenacoxib in blood for the 3 treatments were plotted (Figure 2). For the treatment after food was withheld from the cats, T_{max} was 30 minutes (ie, the first sample collected) in 11 cats and 1 hour (ie, the second sample collected) in 1 cat. For the treatment after cats were fed one-third of the daily ration, a similar pattern was obtained because T_{max} was

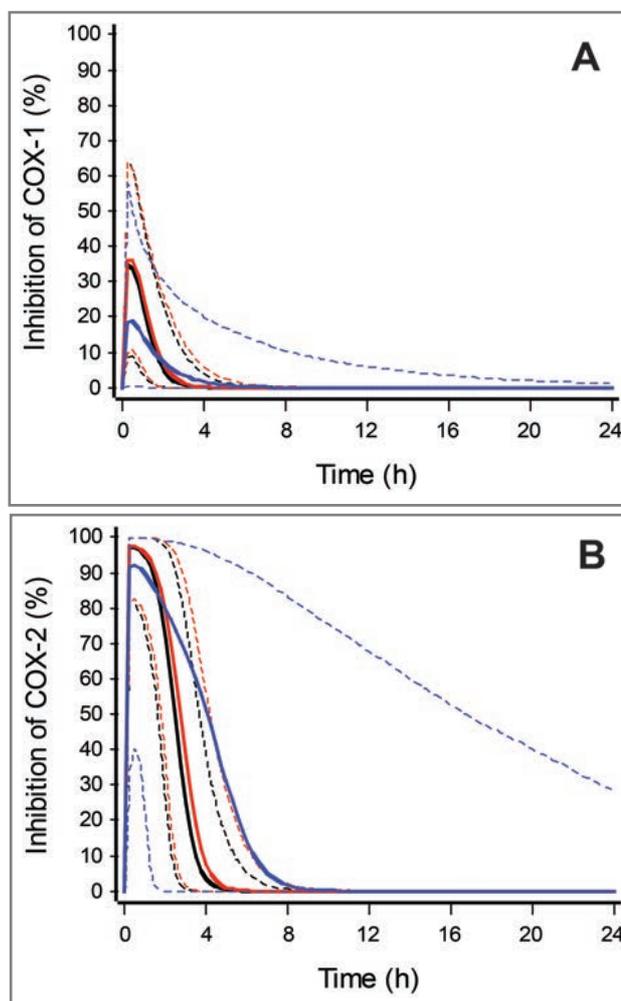


Figure 3—Median (solid line) and 90% PI (dotted lines) values for simulated inhibition of COX-1 after oral administration of 2.4 mg of robenacoxib/kg (A) and COX-2 after oral administration of 1 mg of robenacoxib/kg (B) to cats when food was withheld (black lines) or when cats were fed one-third of the daily ration (red lines) or the entire daily ration (blue lines).

30 minutes in 10 cats and 1 hour in 1 cat, and 1 cat had biphasic absorption with peaks at 1 and 8 hours. For the treatment after cats were fed the entire daily ration, there were 2 patterns for absorption. In 8 cats, absorption was rapid, with T_{max} at 30 minutes in 7 cats and 1 hour in 1 cat. In the 4 remaining cats, blood concentrations increased more slowly, with T_{max} at 2 (1

Table 4—Median and upper limit of the 90% PI for I_{max} and median duration for simulated inhibition of COX-1 and COX-2 after oral administration of robenacoxib to 12 cats when food was withheld or when cats were fed one-third of the daily ration or the entire daily ration.

| Feeding regimen | Robenacoxib dose (mg/kg)* | COX-1 inhibition | | | | COX-2 inhibition | | | |
|------------------|---------------------------|-------------------------|------------------------------|---------------------|-------|-------------------------|------------------------------|---------------------|-------|
| | | Median I _{max} | Upper limit I _{max} | Median duration (h) | | Median I _{max} | Upper limit I _{max} | Median duration (h) | |
| | | | | > 50% | > 10% | | | > 80% | > 50% |
| Food withheld | 1 | 19.9 | 52.2 | 0 | 0.5 | 96.1 | 100 | 1.3 | 2.0 |
| | 2.4 | 33.7 | 70.6 | 0 | 1.0 | 98.2 | 100 | 1.5 | 2.3 |
| One-third ration | 1 | 19.6 | 52.4 | 0 | 0.8 | 96.8 | 100 | 1.5 | 2.5 |
| | 2.4 | 35.9 | 71.2 | 0 | 1.3 | 98.3 | 100 | 2.0 | 2.8 |
| Entire ration | 1 | 11.2 | 46.0 | 0 | 0.3 | 92.7 | 99.9 | 1.3 | 3.4 |
| | 2.4 | 23.9 | 63.8 | 0.3 | 0.8 | 96.5 | 100 | 2.3 | 4.3 |

*Doses of 1 and 2.4 mg/kg were selected because they were the lower and upper value for the recommended dose range of 1 to 2.4 mg/kg.

cat), 3 (2 cats), or 6 (1 cat) hours. Therefore, median T_{max} was 30 minutes (range, 30 minutes to 1 hour) for the food withheld treatment, 30 minutes (range, 30 minutes to 8 hours) for the one-third ration treatment, and 30 minutes (range, 30 minutes to 6 hours) for the entire ration treatment. We did not detect a significant ($P = 1.0$; Mann-Whitney U test) difference in T_{max} between experiments 1 and 2.

Pharmacokinetic variables (Table 2) and bioequivalence comparisons (Table 3) were summarized. The AUC_{0–inf} for the one-third ration and food withheld treatments were bioequivalent (90% CI, 90% to 118%). The C_{max} was similar for these treatments but was not bioequivalent (90% CI, 66% to 162%). The AUC_{0–inf} and C_{max} were not bioequivalent for the entire ration and food withheld treatments. Geometric mean values of MRT and terminal half-life were similar for the 3 treatments; they also were similar to the values reported for these variables in the cats from which food was withheld that received robenacoxib orally in experiment 1.

Pharmacokinetic-pharmacodynamic simulation profiles for simulated inhibition of COX-1 were plotted for oral administration of robenacoxib at a dose of 2.4 mg/kg, which was the upper limit of the recommended dose range of 1 to 2.4 mg/kg (Figure 3). The median I_{max} value was 33.7% for the food withheld treatment, 35.9% for the one-third ration treatment, and 23.9% for the entire ration treatment (Table 4). The predicted median time that there would be > 10% inhibition of COX-1 ranged from 0.8 to 1.3 hours for a dose of 2.4 mg/kg.

Simulated profiles for inhibition of COX-2 were plotted for oral administration of robenacoxib at a dose of 1 mg/kg, which was the minimum recommended dose (Figure 3). There were similar median I_{max} values of 96.1%, 96.8%, and 92.7% for the food withheld, one-third ration, and entire ration treatments, respectively (Table 4). The predicted median time during which there would be > 50% inhibition of COX-2 was 2.0, 2.5, and 3.4 hours for the food withheld, one-third ration, and entire ration treatments, respectively. Slightly longer inhibition times were predicted for a robenacoxib dose of 2.4 mg/kg.

Discussion

In the present study, pharmacokinetic data in cats after IV, SC, and oral administration of robenacoxib

were reported. Analysis of the data after IV administration indicated that the clearance of robenacoxib from blood was 0.44 L/kg/h, with a terminal half-life of 1.5 hours and an MRT of 0.44 hours, which is similar to results of other studies^{1,5} with robenacoxib in cats. Therefore, the terminal half-life of robenacoxib in cats is similar to that of ketoprofen in cats (30 minutes to 1.5 hours) and markedly shorter than that reported for carprofen (19 to 20 hours) or meloxicam (15 hours).¹² However, clearance of robenacoxib from the blood (0.44 L/kg/h [equivalent to 7.3 mL/kg/min]) is classified as a low clearance rate.¹⁰ From these data, the calculated overall body extraction ratio for robenacoxib in cats is 0.05 because the clearance of 7.3 mL/kg/min is exactly 5% of the reported cardiac output for cats (146 mL/kg/min).¹⁰ A body extraction ratio value of 0.05 classifies robenacoxib as having a low extraction rate and is the minimum value desirable for which an orally administered drug can be expected to have reasonable oral bioavailability.¹⁰

Most robenacoxib is retained in the central compartment because of its high degree of binding to plasma proteins, previously reported as > 98% in cats.⁹ In addition, robenacoxib does not penetrate to any great extent into blood cells; the blood-to-plasma concentration ratio for robenacoxib was 0.65 in another study,⁹ and this correlates well with the mean Hct of 0.35 of the cats in the present study.

The volume of distribution allows calculation of the total amount of drug in the body by use of drug concentrations measured in blood or plasma. For drugs such as robenacoxib in which blood and plasma concentrations differ, different values are obtained for pharmacokinetic parameters such as clearance and volume of distribution, depending on whether concentrations measured in blood or plasma are used. Therefore, we reported parameter estimates on the basis of both measured concentrations in blood and estimated concentrations in plasma. The difference in volumes of distribution of robenacoxib in cats as determined on the basis of concentrations in plasma, V_{d,area} (0.61 L/kg), and V_{d,ss} (0.13 L/kg) is explained by elimination of a substantial fraction of administered robenacoxib before pseudoequilibrium is attained.¹³ The V_{d,ss} was only slightly higher than the estimated blood volume of 90 mL/kg in cats, which is consistent with the fact that most robenacoxib resides in the plasma and does not distribute extensively outside the vascular com-

partment in healthy cats. Therefore, the relatively short terminal half-life of robenacoxib in blood of cats can be attributed to the low volume of distribution of this drug; the rate of clearance from blood is low.

After SC injection, bioavailability of robenacoxib was 69% and median T_{max} was 1 hour, compared with 49% and 30 minutes, respectively, after oral administration of robenacoxib to cats from which food was withheld. Therefore, SC and oral routes of administration, the latter for cats from which food was withheld, should provide satisfactory bioavailability and T_{max}.

In experiments 1 and 2, oral administration of robenacoxib tablets concurrent with feeding of the entire daily ration led to reduced bioavailability. Moreover, in experiment 1, consumption of the entire daily ration shortly before robenacoxib administration led to marked interanimal variation in absorption patterns. Bioavailability was extremely low in 5 of 12 cats, and absorption was delayed in 2 other cats. In the remaining 5 cats, bioavailability was much higher than for the other 7 cats, and there was no delay in T_{max}.

Therefore, analysis of the data indicated that administration of robenacoxib with feeding of the entire daily ration may reduce the absorption rate and amount of absorption. No such effects were evident in 11 of 12 cats in experiment 2 when robenacoxib was administered with a smaller amount of food that comprised one-third of the daily ration; in the 12th cat, the effect on absorption was limited to a reduction in rate, with no decrease in the amount of absorption.

Slow esophageal transit of doxycycline and clindamycin has been associated with development of esophageal stricture in cats, which led to recommendations to administer these antimicrobial drugs with food or a small amount of water.^{14,15} Similar precautions should not be necessary for robenacoxib, given that delayed and variable absorption was observed only after coadministration of tablets and a large amount of food and never when food was withheld from cats. Therefore, delayed and variable absorption was probably a result of retention in the stomach and not in the esophagus. In addition, robenacoxib does not typically cause gastrointestinal tract damage. For example, no lesions were detected in the esophagus, stomach, or small or large intestines when high dosages (20 mg/kg/d) were administered daily for 42 days to cats.⁴

In experiment 2, but not in experiment 1, cats from which food had been withheld that received robenacoxib orally also received a small amount of water via syringe after administration of the tablet in the belief that the water would facilitate passage of the tablet into the stomach. There were no significant ($P = 1.0$) differences in T_{max} in the cats from which food had been withheld that received robenacoxib orally in experiments 1 and 2 (median T_{max} was 30 minutes in both experiments). Therefore, administration of a small amount of water does not appear to provide any benefit or to be necessary when administering robenacoxib tablets to cats from which food has been withheld.

The pharmacodynamic and clinical relevance of the pharmacokinetic data for experiment 2 were evaluated via pharmacokinetic-pharmacodynamic simulations by use of the reported relationship between robenacoxib

concentrations in blood and inhibition of COX-1 and COX-2 in cats.¹¹ Because robenacoxib is a selective inhibitor of COX-2, dosage regimens are designed to cause marked inhibition of COX-2 with minimal inhibition of COX-1.

The median predicted I_{max} of COX-2 was high (> 92%) for all 3 feeding regimens. There was no difference in I_{max} or duration of inhibition of COX-2 between administration of robenacoxib to cats when food was withheld or when cats were fed one-third of the daily ration. Administration of robenacoxib in conjunction with feeding the entire daily ration led to a slight reduction in I_{max} but a longer duration of inhibition of COX-2. All 3 feeding regimens were associated with only transient inhibition of COX-1 (median inhibition > 10% did not persist for 1.5 hours for any treatment). Therefore, oral administration of robenacoxib tablets with or without concomitant provision of food in experiment 2 led to marked inhibition of COX-2 at C_{max}, with only minor and transient inhibition of COX-1. The amount of inhibition of COX-1 and COX-2 in the cats in the present study should not cause toxic effects, considering that much higher inhibition (median inhibition of 61% for COX-1 and 99% for COX-2 with 10 mg of robenacoxib/kg, q 12 h for 42 days) was not associated with any detected toxicoses in a safety study⁴ in cats.

It is predicted that optimal efficacy of robenacoxib tablets will be achieved when administered to cats from which food is withheld or to cats concomitantly fed up to one-third of the daily ration. Therefore, for the treatment of acute conditions involving pain and inflammation, it would seem advisable to administer robenacoxib to cats via SC (or IV) injection, orally after food has been withheld, or orally to cats concomitantly provided a relatively small amount of food, which should optimize bioavailability, C_{max}, and T_{max}. Administration of robenacoxib tablets with a large amount of food (eg, the entire daily ration) is not recommended for acute conditions because of variability in absorption. However, administration of robenacoxib tablets with food (a small amount or the entire daily ration) may lead to concentrations sufficient for the treatment of chronic conditions such as degenerative joint disease in cats.

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- a. Selina 3-mix viande, A/S Arovit Petfood, Vejlen, Denmark.
 - b. Excel, Microsoft, Seattle, Wash.
 - c. Novartis Animal Health Inc, Basel, Switzerland.
 - d. Onsior injection, Novartis Animal Health Inc, Basel, Switzerland.
 - e. Onsior tablets, Novartis Animal Health Inc, Basel, Switzerland.
 - f. S-Monovette, Sarstedt AG, Nümbrecht, Germany.
 - g. Data Evaluation In Bioanalytics (DEBA), release 4.1XP, Novartis Pharma AG, Basel, Switzerland.
 - h. SAS Online Doc, version 8, SAS Institute Inc, Cary, NC.
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