Nonlinear mixed-effects pharmacokinetic modeling of the novel COX-2 selective inhibitor vitacoxib in dogs

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Abstract

The objective of this study was to develop a nonlinear mixed-effects model of vitacoxib disposition kinetics in dogs after intravenous (I.V.), oral (P.O.), and subcutaneous (S.C.) dosing. Data were pooled from four consecutive pharmacokinetic studies in which vitacoxib was administered in various dosing regimens to 14 healthy beagle dogs. Plasma concentration versus time data were fitted simultaneously using the stochastic approximation expectation maximization (SAEM) algorithm for nonlinear mixed-effects as implemented in Monolix version 2018R2. Correlations between random effects and significance of covariates on population parameter estimates were evaluated using multiple samples from the posterior distribution of the random effects. A two-compartment mamillary model with first-order elimination and first-order absorption after P.O. and S.C. administration, best described the available pharmacokinetic data. Final parameter estimates indicate that vitacoxib has a low-to-moderate systemic clearance (0.35 L hr⁻¹ kg⁻¹) associated with a low global extraction ratio, but a large volume of distribution (6.43 L/kg). The absolute bioavailability after P.O. and S.C. administration was estimated at 10.5% (fasted) and 54.6%, respectively. Food intake was found to increase vitacoxib oral bioavailability by a fivefold, while bodyweight (BW) had a significant impact on systemic clearance, thereby confirming the need for BW adjustment with vitacoxib dosing in dogs.

1 | INTRODUCTION

Vitacoxib is a selective cyclooxygenase-2 (COX-2) inhibitor from the Coxib group of nonsteroidal anti-inflammatory drugs (NSAIDs). Vitacoxib has been developed and registered in dogs for symptomatic relief of orthopedic and soft tissue surgery, osteoarthritis, and rheumatoid arthritis in China (MOA, 2016). At present, vitacoxib has solely been approved for use in dogs in China.
The pharmacokinetics of vitacoxib have been recently described in young adult horses and in a proof-of-concept study in few Beagle dogs (30 mg P.O., single dose) which was primarily designed to evaluate a new HPLC MS/MS method for bioanalysis (Wang et al., 2018; Xing et al., 2013). However, there is currently no detailed description of vitacoxib pharmacokinetics in dogs following multiple dosing and varying routes of administration.

Nonlinear mixed-effects (NLME) models can leverage information from multiple studies, dosing routes, and administration schedules (Bon et al., 2017). They are also a versatile tool for quantifying both interindividual variability in drug kinetics and population-level parameters (Martinez, Gehring, Mochel, Pade, & Pelligand, 2018; Mochel & Danhof, 2015). The aim of this study was to characterize the pharmacokinetics of vitacoxib in dogs following I.V., P.O., and S.C. dosing using a NLME modeling approach. The influence of age, sex, bodyweight, and food intake on vitacoxib pharmacokinetics was assessed to evaluate the need for dose adjustment of vitacoxib with respect to those covariates in dogs.

2 | MATERIALS AND METHODS

2.1 | Animals

Fourteen healthy adult (7 males + 7 females), 12- to 24-month-old beagle dogs, weighing between 8.8 and 13.7 kg (Table S1), were enrolled in four consecutive and independent pharmacokinetic studies. There was a 14-day washout interval between each 4 studies. Each dog was housed in a single 2 m × 1.5 m isolated box. The animals were acclimated to the enclosures for a minimum of 2 weeks before the start of the study. They were fed with a commercial standard feed and had free access to fresh water. Suitability for inclusion was evaluated by a physical examination, hematology (red and white blood cells counts, Hb, and Hct), clinical chemistry (albumin, total protein, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, and creatinine), and coagulation time parameters. General health observations were performed at least daily during the course of each study.

2.2 | Experimental procedure

Study protocols were reviewed and approved by the Institution Animal Care and Use Committee of the China Agricultural University (Beijing, PR China). Details on the demographics of the study dogs, vitacoxib dose/route of administration, and sampling schedules can be found in Table 1. Venous blood samples were collected from preplaced cephalic vein catheters or by venipuncture collected directly into 2-ml heparinized tubes. All blood samples were centrifuged at 2,280 × g for 10 min, and plasma was stored at −20°C until further analysis.

2.2.1 | Study 1: Single I.V. and P.O. dosing of vitacoxib in fed versus fasted conditions

This three-period study was designed to determine the absolute oral bioavailability of vitacoxib and the effect of food intake on vitacoxib pharmacokinetics in dogs. Six randomly selected, healthy, 12- to 24-month

<table>
<thead>
<tr>
<th>TABLE 1 List of vitacoxib pharmacokinetic studies included for NLME data analysis</th>
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<tr>
<td>Study #</td>
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<tr>
<td>Study 1</td>
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adult Beagles (3 males and 3 females) weighing between 9.0 and 13.8 kg were dosed with a single nominal dose of 30 mg (2.5 mg/kg) P.O. and 1 mg/kg I.V. with a 14-day washout interval between each study period.

1. **Oral dosing.** Vitacoxib was administered orally using a commercial tablet formulation (30 mg/tablet and per dog, Beijing Orbiepharm Co., Ltd.). Tablets were placed on the back of the tongue while swallowing was stimulated with a small amount of tap water. In dogs from the *fasted* group, food was withdrawn for 12 hr overnight and dogs were fed approximately 4 hr after dosing with vitacoxib. *Fed* dogs were dosed with vitacoxib 1 hr after feeding.

2. **I.V. Bolus dosing.** Fasted dogs received a single 1 mg/kg I.V. dose of a vitacoxib commercial formulation (200 mg/10 ml) injected as bolus into the left jugular vein over a 1-min period.

2.2.2 | Study 2: Single P.O. dosing of vitacoxib at 30, 60, and 120 mg in fed conditions

This three-period study was designed to evaluate the disposition kinetics of vitacoxib after oral dosing in dogs. Six healthy 12- to 24-month adult Beagles (3 males and 3 females) weighing between 8.9 and 13.7 kg were used. Dogs were dosed 1 hr after feeding and received a single oral tablet of vitacoxib at 30 mg, 60 mg, and 120 mg in three different study periods, with a 14-day washout interval in between.

2.2.3 | Study 3: Multiple P.O. dosing of vitacoxib at 60 mg in fed conditions

This study was designed to report the steady state pharmacokinetics of vitacoxib after multiple oral dosing with vitacoxib in dogs. Six healthy 12- to 24-month adult Beagles (3 males and 3 females) weighing between 8.9 and 13.7 kg were dosed with one vitacoxib 60 mg tablet 1 hr after feeding and for seven consecutive days.

2.2.4 | Study 4: Single I.V. and S.C. dosing of vitacoxib in fed conditions

This four-period study was designed to determine the absolute bioavailability of vitacoxib after S.C. dosing. Eight healthy adult Beagles (4 males and 4 females) weighing between 8.8 and 13.5 kg were dosed with a single nominal dose of 2, 4, and 6 mg/kg (S.C.) under the loose skin over the shoulder and 1 mg/kg (I.V.). For I.V. dosing, a vitacoxib commercial formulation (200 mg/10 ml) was injected as bolus into the left jugular vein over a 1-min period. A 2-week washout period elapsed between each dosing with vitacoxib.

2.3 | Data analysis

Plasma samples were analyzed using a validated UPLC-MS/MS (Waters Acquity UPLC and Water Quattro Premier, Waters Co.) method after precipitation of proteins by acetonitrile as previously described (Wang et al., 2017). Briefly, frozen plasma samples were thawed and vortexed, and 100 µl plasma was mixed with methyl tert-butyl ether, followed by vortex-mixing. The upper organic layer was collected, while the precipitate was re-extracted with the same procedure described above. After the second extraction, the supernatant was combined and evaporated to dryness with nitrogen gas. Thereafter, samples were reconstituted in 1 ml of methanol-water (1:1 v/v). The supernatant was collected to the UPLC-MS/MS system for analysis (Waters Acquity UPLC and Water Quattro Premier, Waters Co.). The mobile phase consisted of 0.1% formic acid (solvent A) and acetonitrile (solvent B) with a flow rate of 0.4 ml/min. The gradient elution program was as follows: 0–1.5 min. 10% solvent B; 1.51–6.5 min, 85% solvent B; and 6.51–8 min 10% solvent B. The mass spectrometers were operated in the positive ion detection mode with the capillary voltage set at 3.1 kV. Other parameters were as follows: source temperature, 120°C and desolation by gas flow, 800 L/hr. The source collision induced dissociation voltage was 25 V. The quantification and qualitative ions were m/z 347.9/269.03 and m/z 347.9/192.03 for vitacoxib and m/z 382.0/362.0 for celecoxib (internal standard).

The bioanalytical method was thoroughly validated with a lower limit of quantification (LLOQ) of 0.5 ng/ml. The calibration curves were in good linearity cover the range of 1 ~ 1,000 ng/ml (R² > 0.99). The interday and intraday coefficients of variation at three different concentrations (3, 80 and 750 ng/ml) were all below 15%; meanwhile, the mean recoveries ranged from 81.4% to 95.9%. All analyses complied with established guidelines on bioanalytical method validation (FDA, 2013).

2.4 | NLME model building

All data from the four pharmacokinetic studies were pooled together for nonlinear mixed-effect analysis. Vitacoxib plasma concentration time courses from P.O., I.V., and S.C. dosing were analyzed simultaneously using the stochastic approximation expectation maximization algorithm implemented in the Monolix Suite 2018R2 (Lixoft). Individual model parameters were obtained post hoc using the mean of the full posterior distribution.

Similar to Sheiner and Ludden report (Sheiner & Ludden, 1992), mathematical models were written using the following format:

\[ y_{ij} = F(\phi_i, t_{ij}) + G(\phi_i, t_{ij}, \beta) \cdot \epsilon_{ij}, \]

where \( y_{ij} \) is the observed variable (e.g., vitacoxib) measured on the ith individual at time \( t_{ij} \), \( \phi_i \) is the vector of individual parameters, \( F(\phi_i, t_{ij}) \) is the value of that observed variable at time \( t_{ij} \) for an individual with parameters \( \phi_i \), and \( \epsilon_{ij} \) is an independent random variable. The function \( G(\phi_i, t_{ij}, \beta) \) is the standard deviation of the error of a given measurement at time \( t_{ij} \). In population modeling, \( F(\phi_i, t_{ij}) \) is known as the structural model (error-free), while \( G(\phi_i, t_{ij}, \beta) \) is the residual error model (combining unexplained variability and measurement noise). \( \mu \) represents the typical value.
(population average) of a model parameter. The sources of variation between the individual parameters $\phi_i$ can be further explained by population characteristics (i.e., covariates) that can be included additively or proportionally to $\mu$. The independent random variables $\eta_i$ represent the unexplained difference between the value of the individual parameters $\phi_i$ and their average $\mu$. The random variables $\epsilon_i$ and $\eta_i$ were assumed to be normally distributed with mean value 0 and variance–covariance matrix $\sigma^2$ and $\omega^2$, while $y_{ij}$ and $\phi_i$ were log-normally distributed.

2.5 | Model evaluation

Convergence of the stochastic approximation expectation maximization (SAEM) algorithm was evaluated by inspection of the stability of the fixed and random effect parameter search and the log-likelihood estimate after the exploratory period of the algorithm (i.e., after 1,000 iterations of SAEM). Standard goodness-of-fit diagnostics, including individual predictions versus observations, the distributions of weighted residuals (IWRES), and normalized prediction distribution errors (NPDE) were used to assess the performances of the candidate models. Prediction distributions from 500 Monte Carlo simulations were used to evaluate the ability of the final model to reproduce the variability in the observed pharmacokinetic data. Residual error estimates from the mathematical models were used as supportive information for evaluation of lack of fit. Normality and independence of residuals were assessed using histograms, quantile–quantile plots, and autocorrelation of conditional weighted residuals. For converging models with satisfactory goodness-of-fit diagnostics, model selection was based on the Bayesian information criteria (BIC) and the precision of the model parameter estimates. The BIC was selected over the Akaike information criterion as it tends to select simpler and more parsimonious models (Mould & Upton, 2013).

All interindividual variability and interoccasion variability were modeled using log-normal distributions except for bioavailability ($F$), which was modeled using a logit-normal function to bound predictions between 0 and 1.

2.6 | Handling of below limit of quantification (BLQ) data

Data below the LLOQ were modeled by adding to the likelihood function a term describing the probability that the true observation lies between zero and the LLOQ. For the calculation of the likelihood, this is equivalent to the M3 method implemented in NONMEM.

2.7 | Parameter correlation estimates

Visual inspection of the $\eta$ versus $\eta$ scatterplot was used to evaluate correlations between model parameters. In agreement with previous literature (Lavielle & Ribba, 2016; Pelligand, Soubret, King, Elliott, & Mochel, 2016), several samples of the posterior distribution obtained at last iteration of the SAEM algorithm, rather than the empirical Bayes estimate (EBE), were used to assess the correlation between model parameters.

2.8 | Inclusion of covariate relationships

The effect of two continuous variables (BW and age) and two factors (sex and feeding status) on parameters estimates of the base NLME model was evaluated using the automated Pearson’s correlation test and ANOVA method implemented in Monolix 2018R2. $p < .05$ were considered as statistically significant for inclusion of a covariate effect in the final NLME model. Age and BW were normalized by their median value and log-transformed during the covariate search.

3 | RESULTS

3.1 | Animal safety

No adverse drug effects were reported after vitacoxib dosing in any of the four pharmacokinetic studies.

3.2 | Pharmacokinetic model

3.2.1 | Model evaluation

Only 3.6% (49/1351) data were found to be below the LLOQ of the UPLC-MS/MS validated method. A two-compartment mammillary disposition model with first-order elimination and first-order absorption for the P.O. and S.C. route, best described the pharmacokinetics of vitacoxib in plasma (Figure 1). A combined error model with an additive and a proportional error term was used to account for the residual noise in the measurement of vitacoxib in plasma. The robustness and predictive performances of the final model were
FIGURE 2 Standard goodness-of-fit (sGOF) diagnostics: individual predictions versus observations (log scale). Upper panel: I.V. (#RTE: 1); middle panel: P.O. (#RTE: 2); lower panel: S.C. (#RTE: 3). The robustness of fit and predictive performances of the final model were supported by the inspection of the sGOF plots. Blue dots: observations; green line, identity line; dotted black lines: 90% prediction interval; red dots: censored (i.e. below the quantification limit) data. In agreement with recent guidelines from Nguyen et al. (2017), observations are displayed on a log scale to better evaluate the quality of fit.
supported by the inspection of the standard goodness-of-fit diagnostics (Figure 2) and the model residuals (Figure S1A). The normality of the random effects was further confirmed by the distribution of the $\eta_i$ around a mean value of 0 (Figure S1B). Overall, the model was able to reproduce the individual experimental data for all the dosing schedules with excellent accuracy, as shown by the quality of the individual fits (Figure 3). The correlation matrix of the random effects (i.e., the $\eta_i$) can be found in Figure 4. All correlation coefficients were estimated to be low ($r \leq 0.15$), hereby confirming the robustness and identifiability of the estimated parameters from the final selected model.

### 3.2.2 Parameters estimates

Population pharmacokinetic parameter estimates and their related variances are summarized in Table 2. For most of the model parameters, the precision of the final estimates was considered satisfactory (RSE $\leq 35\%$). The systemic total body CL of vitacoxib was estimated to be low to moderate (0.35 L kg$^{-1}$ hr$^{-1}$), according to previous definition by Toutain and Bousquet-Melou (2004a), while the vitacoxib steady state volume of distribution was estimated to be large (6.43 L/kg), with the peripheral compartment occupying most of the distribution of vitacoxib in dogs ($V_2 = 5.51$ L/kg).

The global extraction ratio of vitacoxib ($E$) calculated as $CL/Q_c$ (with cardiac output $Q_c$ (ml kg$^{-1}$ min$^{-1}$) approximated by the formula: $Q_c = 180^*BW^{-0.19}$; Toutain & Bousquet-Melou, 2004a) was estimated to be low ($E = 0.05$). Finally, the absolute bioavailability of vitacoxib was estimated to be low (10.5% in fasted conditions) to moderate (54.6%) for oral and subcutaneous dosing, respectively. Food intake was found to significantly increase vitacoxib oral bioavailability by a fivefold ($p < .001$), while BW had a significant effect on vitacoxib systemic clearance ($p = .001$). Results from the automated covariate analysis in Monolix 2018R2 suggested that neither age nor sex had a statistically significant effect on the pharmacokinetics of vitacoxib in dogs.

Of note, most of the variance in the estimated model parameters was found to originate from interoccasion (i.e., within-subject) variability, with the volume of the peripheral compartment driving most of the between-subject variability (Table 2). In the course of model building, the statistical model was first parameterized using

**FIGURE 3** Individual predictions of vitacoxib plasma concentration in healthy beagle dogs from the final selected model. Scatter plot of observed (blue dot) and predicted (dashed purple line) individual vitacoxib concentration versus time after dosing. The full model was able to describe the individual time course of vitacoxib for all dosing schedules with excellent accuracy, as shown by the quality of the individual fits. Dosing time at left limit of x-axis.
FIGURE 4  Correlation matrix of the random effects (i.e., the $\eta$). All correlation coefficients were estimated to be low ($r \leq .15$), thereby confirming the robustness and identifiability of the estimated parameters from the final selected model.

TABLE 2  Estimated model parameters and their associated interindividual and interoccasion variability for vitacoxib pharmacokinetics in dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Point estimate</th>
<th>Relative standard (error %)</th>
<th>IIV (%)</th>
<th>IOV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic clearance</td>
<td>CL</td>
<td>L hr$^{-1}$ kg$^{-1}$</td>
<td>0.35</td>
<td>14</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>Coefficient of the covariate relationship (BW_CL)</td>
<td>$\beta_{CL}$</td>
<td>—</td>
<td>1.8</td>
<td>31</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Absorption (P.O)</td>
<td>$Ka_1$</td>
<td>1/h</td>
<td>0.32</td>
<td>11</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>Absorption (S.C)</td>
<td>$Ka_2$</td>
<td>1/h</td>
<td>0.40</td>
<td>11</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>Central compartment volume of distribution</td>
<td>V1</td>
<td>L/kg</td>
<td>0.92</td>
<td>4</td>
<td>—</td>
<td>41</td>
</tr>
<tr>
<td>Peripheral compartment volume of distribution</td>
<td>V2</td>
<td>L/kg</td>
<td>5.51</td>
<td>33</td>
<td>198</td>
<td>107</td>
</tr>
<tr>
<td>Intercompartmental clearance</td>
<td>Q</td>
<td>L hr$^{-1}$ kg$^{-1}$</td>
<td>0.54</td>
<td>17</td>
<td>46</td>
<td>104</td>
</tr>
<tr>
<td>Bioavailability (P.O, fasted)</td>
<td>F1_Fasted</td>
<td>%</td>
<td>10.5</td>
<td>16</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>Bioavailability (P.O, fed)</td>
<td>F1_Fed</td>
<td>%</td>
<td>54.6</td>
<td>16</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>Bioavailability (S.C)</td>
<td>F2</td>
<td>%</td>
<td>26.7</td>
<td>12</td>
<td>—</td>
<td>22</td>
</tr>
</tbody>
</table>

Abbreviations: #, fixed parameter value; —, random effect value fixed to 0; IIV, interindividual variability, expressed as CV%; IOV, interoccasion variability, expressed as CV%; N/A, not applicable; P.O, Per Os; RSE, relative standard error; S.C, subcutaneous.

Food intake was found to have a significant effect on vitacoxib oral bioavailability ($p < .001$), while BW had a significant effect on vitacoxib systemic clearance ($p = .001$). More details on the abbreviated parameters can be found in the legend of Figure 1.
a full matrix of interindividual and interoccasion random effects. However, when estimating parameters of the full variance–covariance matrix, several interindividual (IIV) random effects were found to be convergent on zero (<1e-4) and were estimated with low precision (i.e., high RSE%). This finding suggested that the observed data were too sparse to correctly identify the IIV components of these parameters and that these random effects had little impact on the estimated total variability. Consequently, IIV terms which were convergent on zero were removed from the statistical model, which improved model stability while having little to no impact on final model parameter estimates for the fixed-effects.

3.2.3 | Model simulations

Prediction distributions (from the 2.5th to 97.5th percentile) derived from 500 Monte Carlo simulations confirmed the good performances of the final selected model which was able to reproduce the variability in the observed disposition kinetic data of vitacoxib following I.V., S.C., and P.O. dosing (Figure 5).

4 | DISCUSSION

To our knowledge, this is the first comprehensive characterization of vitacoxib pharmacokinetics in dogs. Vitacoxib doses ranging from 1 to 10 mg/kg BW were administered in different routines in 4 separate studies using 14 dogs (7 females + 7 males) during 1-7 days. NLME models are a versatile tool for quantifying variability in drug disposition and response as a function of individual patient characteristics (i.e., covariates, such as age, sex, and BW; Bon et al., 2017). Another advantage of the NLME approach is that pharmacokinetic data from various studies can be pooled together for analysis, allowing for the estimation of interindividual and interoccasion (i.e., within-subject) variability in a single run. Leveraging the properties of the mixed-effects approach, the pharmacokinetics of vitacoxib after intravenous and extravascular dosing, single and multiple administrations and under fasted or fed conditions, were evaluated simultaneously.

A two-compartmental mammillary disposition model with first-order elimination and first-order absorption after P.O. and S.C. dosing, best described the available pharmacokinetic data. Parameter estimates of the final NLME model suggest that vitacoxib has a low-to-moderate systemic clearance (0.35 L hr⁻¹ kg⁻¹) associated with a low extraction ratio (0.05), but a relatively large volume of distribution (6.43 L/kg). As expected, bodyweight had a significant influence (p = .001) on systemic clearance, thereby confirming the need for BW adjustment with vitacoxib dosing in dogs. The estimated volume of distribution of vitacoxib in dogs was in line with previous descriptions in other species such as rabbits (7.8 L/kg; Wang, Xue, et al., 2019) and greater than reported values in cats (1.2 L/kg; Wang, Gong, et al., 2019). As a poorly water-soluble drug, vitacoxib has a high binding affinity to adipose tissues, which could explain, at least partially, the large estimated volume of the peripheral compartment (Greenblatt, 1985; Toutain & Bouquet-Melou, 2004b). This large distribution volume results in a relatively long elimination half-life for vitacoxib in dogs (ca. 12.7 hr, calculated as 0.693 x Volume of distribution/Clearance).

Of note, the total variance in vitacoxib disposition kinetics was estimated to be large, combining both interindividual and interoccasion (i.e., within-subject) variability on some model parameters, such as CL, V2, and Q (see abbreviations in Table 2). This is in agreement with earlier findings from other Coxibs such as robenacoxib, celecoxib, and mavacoxib that also display high within and/or between-dog variability in their pharmacokinetics (Fink et al., 2013; Fleischer, Sharkey, Sharkey, Mealey, Ostrander, & Martinez, 2008; Paulson et al., 1999).

The estimated low bioavailability of vitacoxib after oral dosing (~10% in fasted conditions) was unexpected and could be related to its poor water solubility (Wang et al., 2018), which would affect dissolution in the gastrointestinal tract and subsequent absorption of the active pharmaceutical ingredient API (Song, Hua, Peng-Yue, Zhang, & Hou, 2013; Zeng, Huang, Li, Zhu, & Feng, 2014). Interestingly, food intake was found to increase vitacoxib oral bioavailability by a ~5-fold (p < .001), which is consistent with earlier observations from other Coxibs (i.e., mavacoxib, celecoxib, and deracoxib) in dogs (Cox et al., 2010; Paulson et al., 2001). Feeding could improve vitacoxib bioavailability (from 10.5% to 54.6%) by increasing gastric residence time, allowing more time for tablet dispersion and drug dissolution. Alternatively, food intake can also increase dissolution of vitacoxib through meal-stimulated secretion of bile salts. This has obvious consequences for dosing recommendation of vitacoxib in dogs, as co-administration with food significantly improves systemic exposure and, potentially, therapeutic effect of the NSAID.

Of note, the S.C absolute bioavailability of vitacoxib was also relatively low (26.7%), which again could be related to the high binding affinity of the drug for adipose tissues, as a significant amount of vitacoxib would be stored in the adipose and not be available to the systemic circulation. Additional ADME studies are warranted to better characterize the tissue distribution of vitacoxib in dogs.

4.1 | Limitations

A main limitation of this work is that age and breed differences could not be accounted for as covariates in the pharmacokinetic analysis. The relatively narrow range of age values has likely hampered our ability
to identify this parameter as a significant covariate in the final model. Importantly, although there is currently limited information on pharmacogenetic differences between dog breeds in the literature, Coxibs such as celecoxib and mavacoxib are known to display large within and between-breed variability in dogs (Cox, Liao, Payne-Johnson, Zielinski, & Stegeman, 2011). Therefore, differences in pharmacokinetics between laboratory beagle dogs and client-owned animals will need to be further investigated in clinical studies.

5 | CONCLUSION

In summary, a two-compartmental disposition model with first-order elimination and first-order absorption after P.O. and S.C. dosing best described the pharmacokinetics of vitacoxib in dogs. Vitacoxib has a low systemic clearance and a low global extraction ratio but is largely distributed, probably due to its lipophilic nature. The oral bioavailability of vitacoxib was estimated to be low to moderate after fasted and fed conditions, respectively. Results from the covariance analysis confirmed the need for BW adjustment with vitacoxib in dogs and suggest that vitacoxib be given with food to increase its oral bioavailability.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest. Jing Lin is employer of Beijing Orbiepharm.

AUTHOR CONTRIBUTION

All authors contributed to the preparation of the manuscript. XC contributed to the design and execution of the experiments. JPM performed the NLME data analysis. JL provided the test drug. PS, XG, and JQ contributed to the animal experiments. JW was involved in the execution of the study and the interpretation of study results. All authors have read and approved the final manuscript.

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REFERENCES


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