Evaluation of factors important in modeling plasma concentrations of tetracycline hydrochloride administered in water in swine

Sharon E. Mason, DVM, PhD; Glen W. Almond, DVM, PhD; Jim E. Riviere, DVM, PhD; Ronald E. Baynes, DVM, PhD

Objective—To model the plasma tetracycline concentrations in swine (*Sus scrofa domestica*) treated with medication administered in water and determine the factors that contribute to the most accurate predictions of measured plasma drug concentrations.

Sample—Plasma tetracycline concentrations measured in blood samples from 3 populations of swine.

Procedures—Data from previous studies provided plasma tetracycline concentrations that were measured in blood samples collected from 1 swine population at 0, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, and 104 hours and from 2 swine populations at 0, 12, 24, 48, and 72 hours hours during administration of tetracycline hydrochloride dissolved in water. A 1-compartment pharmacostatistical model was used to analyze 5 potential covariate schemes and determine factors most important in predicting the plasma concentrations of tetracycline in swine.

Results—2 models most accurately predicted the tetracycline plasma concentrations in the 3 populations of swine. Factors of importance were body weight or age of pig, ambient temperature, concentration of tetracycline in water, and water use per unit of time.

Conclusions and Clinical Relevance—The factors found to be of importance, combined with knowledge of the individual pharmacokinetic and chemical properties of medications currently approved for administration in water, may be useful in more prudent administration of approved medications administered to swine. Factors found to be important in pharmacostatistical models may allow prediction of plasma concentrations of tetracycline or other commonly used medications administered in water. The ability to predict in vivo concentrations of medication in a population of food animals can be combined with bacterial minimum inhibitory concentrations to decrease the risk of developing antimicrobial resistance. (*Am J Vet Res* 2012;73:1641–1649)

Medications administered in water have been used extensively in the livestock industries to treat populations of animals, yet few pharmacokinetic studies[1–3] have been conducted on medications administered in water. This is likely related to concerns with individual variability and the inability to adequately model pharmacokinetics of drugs for a population of animals with traditional techniques.[4] One potential technique that could provide insight and improved pharmacokinetic modeling is population-based modeling with nonlinear mixed effects.[5] Few population pharmacokinetic studies[6–10] have been performed in veterinary medicine and none on medications administered via water. Only 1 study[6] has investigated the population pharmacokinetics of doxycycline coadministered with paracetamol

Abbreviations

AIC	Akaike information criterion
BIC	Bayesian information criterion
CV	Coefficient of variation
F	Bioavailability
FOCE	First-order conditional estimate
Ke	Elimination constant
Kel	Elimination rate constant
LL	Log likelihood value
MIC	Minimum inhibitory concentration
Vd	Volume of distribution

Received June 3, 2011.
Accepted November 3, 2011.
From the Department of Comparative Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606. Dr. Mason's present address is Department of Biological Sciences, College of Arts and Sciences, Campbell University, Buies Creek, NC 27506. Dr. Riviere's present address is College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506.
This manuscript represents a portion of a dissertation submitted by the first author to the North Carolina State University Department of Comparative Biomedical Sciences as partial fulfillment of the requirements for a Doctor of Philosophy degree.
Supported by the Food Animal Residue Avoidance Databank and Pfizer Animal Health.
Address correspondence to Dr. Mason (masons@campbell.edu).

(acetaminophen) in a slurry (liquid) fed to swine. That study[6] examined the effects of consuming a slurry diet and major factors affecting the pharmacokinetics of the 2 medications administered concurrently in diseased pigs; however, neither doxycycline nor paracetamol is approved in the United States for administration in swine. Also, these medications were not given in water. The pharmacokinetics of tetracycline are different from those of doxycycline and have been found to be affected by food; therefore, the pharmacokinetics of tetracycline administered in water require further investigation.

Two studies[2,11] have investigated multiple-dose regimens of tetracycline in water. Mason et al[2] reported the plasma pharmacokinetic parameters for tetracycline given at 3 concentrations in water to individually housed swine (*Sus scrofa domestica*), and Dorr et al[11] investigated the pharmacoepidemiology of tetracycline administered in water in commercially housed animals. Both studies[2,11] determined that the predictability of plasma concentrations was extremely variable, and neither method adequately explained the potential causes for this variability.

An understanding of the factors that influence the pharmacokinetics of medications given in water in vivo is important because of the frequency of antimicrobials given by this method in the swine industry, both in the United States and worldwide.[12] The purpose of the study reported here was to determine whether the use of a nonlinear mixed-effects pharmacokinetic model could elucidate factors most important in predicting water concentrations of tetracycline in a population of swine between 8 and 13 weeks of age.

Materials and Methods

Pharmacokinetic program and design—A population pharmacokinetic program[a] was used to conduct all of the pharmacokinetic analyses.[13] A nonlinear mixed-effects model that uses written code (ie, not a precoded model from the program database) was designed, improved, and compared by means of 3 data sets from independent populations of animals in our research facility[2] or from a commercial farm.[11] Data collected by Mason et al[2] (training set) as part of another study were initially used to develop a population-based pharmacokinetic model to mimic observed tetracycline concentrations in swine. The training set data were used to develop the basic structural (1-compartment open) model and select covariate factors that were included (body weight or age of pig, ambient temperature, concentration of tetracycline in water, and water use per unit of time). The training set was used to develop the 1-compartment model with 5 covariate model possibilities, which were then tested on the basis of their ability to accurately simulate data independently collected by Dorr et al[11] as part of their study. The 2 data sets collected by Dorr et al[11] were compared with the best models for validation (150 µg/mL data set) and simulation (80 µg/mL data set). Plasma concentrations from each data set were considered the dependent variables for modeling purposes. The pharmacokinetic program was run with FOCE via the Lindstrom-Bates algorithm.[14] This algorithm was used for early model selection due to the time to run the FOCE–extended least squares algorithm and independently compared with the FOCE–extended least squares models to determine the best fit.[15] The final model predictions and selection for figures were determined with FOCE via the Lindstrom-Bates algorithm because there was no obvious model fit benefit from the extended least squares algorithm.

Structural model determination—Data on tetracycline pharmacokinetics[16,17] suggested that either a 1- or 2-compartment model would be accurate to represent the plasma concentration data. Therefore, both 1- and 2-compartment models were initially considered. The initial pharmacokinetic parameters included in the structural model were Vd of the plasma compartment, F, and Kel.[18,19] A priori parameter estimates from the literature were used for the initial values of these parameters.[2] The parameter limits were set for each parameter on the basis of physiologically reported maximum values with a minimum set to 0 for each parameter.[2,3,17] After comparing the model results for 1- and 2-compartment models, it became apparent with the 2-compartment model that parameter estimates could not be accurately determined. Large SDs and CVs were present for all parameters. This variability was due to a lack of data for the secondary compartment. Therefore, the 1-compartment model was chosen for modeling data.

The parameter estimates for the 1-compartment model were set on the basis of the training set data population mean for each parameter (F, Kel, and Vd). Of all the model parameters for the training and validation data sets, F was found to be most consistent and ranged only from approximately 0.05 to 0.08 for all data sets when included in the structural model as a variable parameter. These model parameter estimates for F are

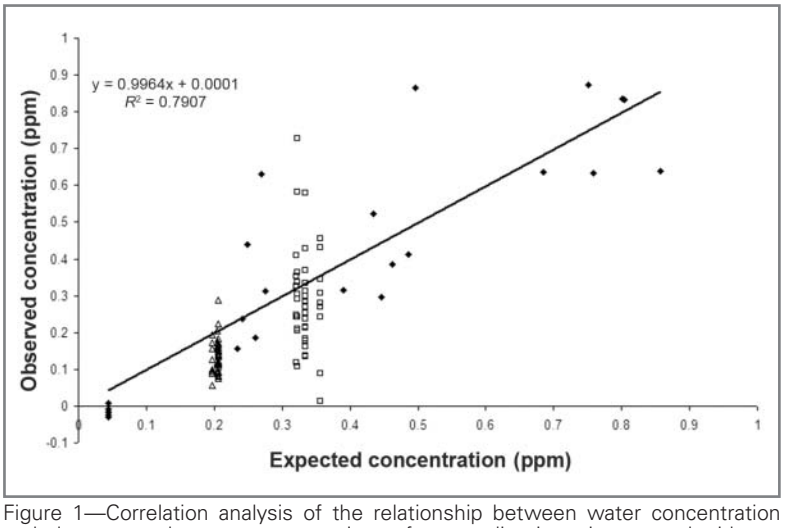

Figure 1—Correlation analysis of the relationship between water concentration and plasma steady state concentrations of tetracycline in swine treated with tetracycline in water. Diamonds represent plasma concentrations from Mason et al.[2] Squares represent pigs exposed to approximately 150 µg of tetracycline/mL during the winter. Triangles represent pigs exposed to 80 µg of tetracycline/mL (Dorr et al[11]). The straight line is the model that predicts data from Mason et al.[2] Notice that the Dorr et al[11] data are typically below the line.

close to reported literature values of 0.06 (6% F) in fed swine exposed to tetracycline.[2,17] Therefore, F was set as a fixed value of 0.06 for the training and validation sets. By fixing this parameter, parameter degeneration was reduced for the rest of the model and a better fit was achieved for most of the data.[20]

Covariate selection—Covariates were selected on the basis of statistical analysis[b] (data not included) and graphic comparisons of residuals before inclusion in the model. A normal or log-normal distribution was assumed for all data distributions on the basis of graphic analysis and lack of improved fit via nonparametric statistical analysis.

The initial linear equation predicted by Mason et al[2] was a direct correlation between water concentration and plasma concentrations in treated pigs and was set as the default or null model (which included tetracycline concentration in the water as the only covariate for dose). Other potential factors, including serum creatinine concentration and urine specific gravity, were tested as covariates (as surrogates) for F and clearance. Serum creatinine concentration (often a covariate for clearance) was found to be nonpredictive because all values for the population of animals were within 0.1 mmol/dL of each other. Urine specific gravity was also not predictive due to highly concentrated urine in all animals. Finally, body weight was tested as a covariate and found to be predictive of water use and Vd. Therefore, body weight was used as a covariate for 2 factors: volume of the central compartment (Vd) and tetracycline dose.

Covariate model design—Based on both graphic and ANOVA comparisons, measured water use proved to be a useful parameter, as did individual and expected body weights. The water use in the training data set was high, compared with water use expected on the basis of other investigations.[21,22] The plasma concentrations of the other 2 populations were less than that of the predicted linear model by Mason et al[2] (**Figure 1**). Based on this information and previous studies,[23] water use was positively correlated with increased temperatures. Thus, temperature was included in the covariate models with a diurnal pattern variation of peak in the day and decrease at night. Of all the variability in the proposed pharmacokinetic models, the most important variable with regard to data fit was the dose of tetracycline for each animal. The dose of medication was determined by the amount of water use because tetracycline was only available in water. Therefore, a method of integration of the total water used during a 24-hour period for 2 days was used to predict the tetracycline dose for each animal on the basis of the training data set values. To account for this amount of medication, the covariate pharmacokinetic models included a variable mean population water use rate, calculated from known drinking rates, which was used to integrate the total dose of medication during each 24-hour time period, correlate it with collected data on each animal, and adjust it on the basis of the temperature, when appropriate. The mean population water use rate variable had a major effect on the 5 covariate equations and the results of the models. The covariate models were summarized (**Appendix**).

Model selection and validation—The 5 covariate models were compared with the linear model and collected data. Goodness of fit of the models was assessed via 3 criteria. First, the model fit was assessed subjectively on the basis of graphic appearance of the data and predictions. Secondly, the AIC, BIC, and LL values for each of the models were compared with one another.[24–27] Finally, each model's parameter estimates were compared with literature parameter values for animals of similar ages.[2,3,16,17,28] In this final assessment, the CVs and predicted SDs of the parameter estimates were considered in determining the goodness of fit of each model. Models were easily compared via the AIC, BIC, and LL values. The smallest value attained for each criterion is considered the best fit. Secondly, if a model predicted 1 or more parameter values outside of the known physiologic range, it was eliminated from further comparisons. Finally, the graphic fit was observed subjectively to verify that the model was in fact credible. The ability of a model to predict changes in plasma concentrations or the lack of its ability to do so would alter the model's final ranking (from better to worse).

Results

Initial model development with the training data set selected between a 1- and 2-compartment model. Although the 2-compartment model was able to fit the data, the AIC values were significantly higher for this structural model and CVs for all parameter estimates were approximately 10 times the CVs for parameters of the 1-compartment model. Therefore, the 1-compartment model was selected.

The 5 covariate models were then analyzed with the training set data in a 1-compartment model and

Table 1—Parameter estimation for models 1, 2, and 5 with CVs for training data (Mason et al[2]) in a study modeling plasma concentrations of tetracycline in swine treated with tetracycline in water.

	Model 1		Model 2		Model 5	
Population parameter	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**
Volume (mL/kg)	963	18.9	792	20	2,577	15.5
Kel (1/h)	0.253	18.8	0.298	19.6	0.088	16.1
drate	203	9.8	8.32	10.1	5.22	27.6
Concentration SD (μg/mL)	0.192	5.0	0.189	5.0	0.198	5.5
Water use SD (mL)	1,512	14.0	1,604	13.3	1,318.42	17.4

CV (%) = Coefficient of variation of the parameter estimate. drate = Drinking rate; units for drate are mL/h for model 1 and mL/(h•kg) for models 2 and 5.

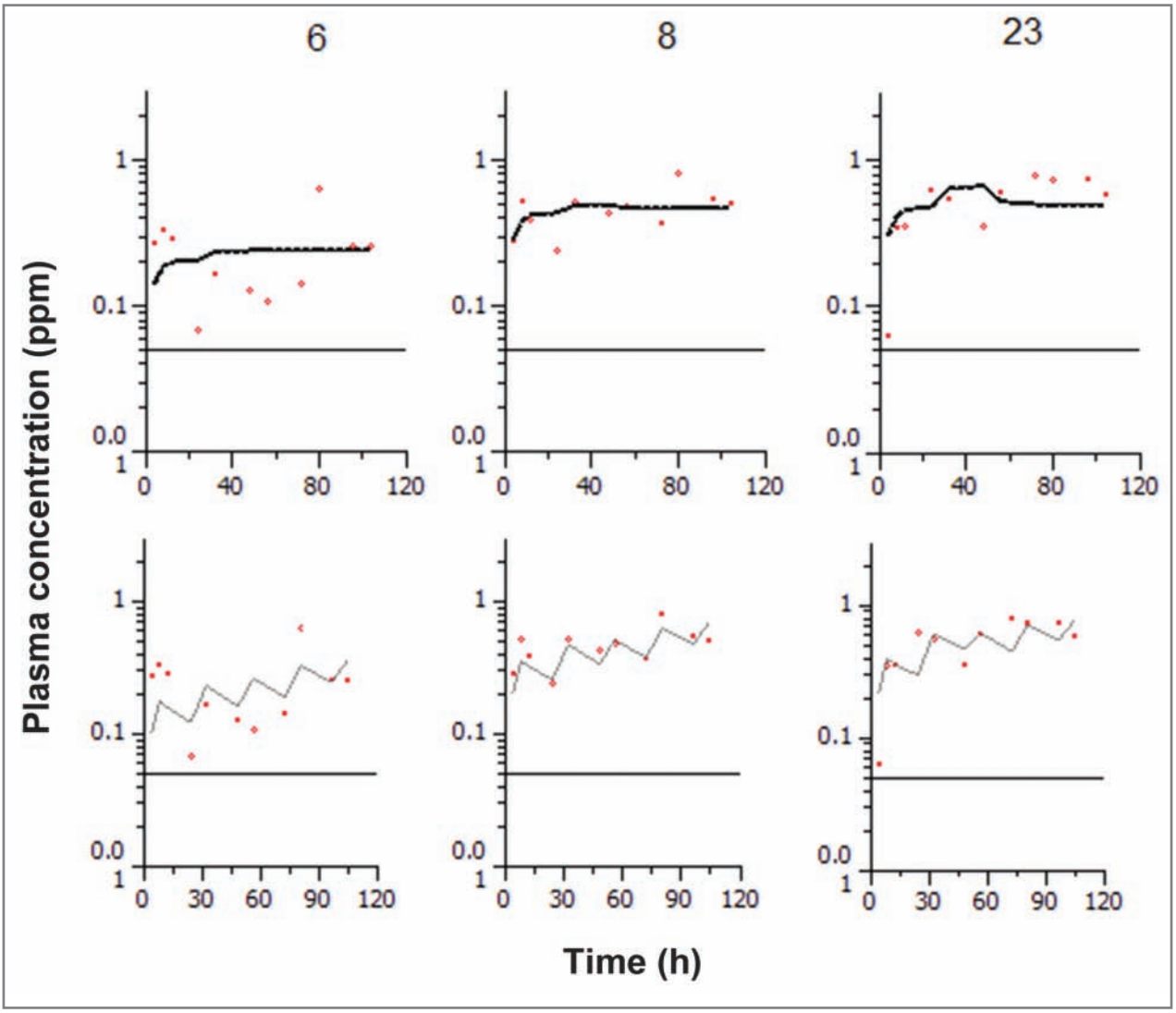

Figure 2—Model estimation of training set plasma concentrations of tetracycline in swine. All graphs are on a semilogarithmic scale. Numerals 6, 8, and 23 represent individual animals. The top panels represent model estimations for model 2, and the lower panels represent model estimations for model 5. Data points (red) indicate actual plasma concentrations from the individual animal, and the solid line is the predicted plasma concentration. The solid horizontal line represents the lowest quantifiable concentration of tetracycline in plasma. Notice poor fit of the data for animal 6, typical fit of the data for animal 8, and good fit of the data for animal 23.

compared by use of the training data and the criteria for model ranking. Based on AIC, BIC, and LL values, models 3 and 4 were removed from the model selections (Appendix). The other 3 models had similar fits, with model 1 having the lowest score for each of the AIC, BIC, and LL tests. The graphic fits of models 1 and 2 appeared to mimic an asymptotic fit, which results in a plateau of the dose over time and which is commonly used to model multiple-dose regimens.[4] Contrarily, model 5 had a wave pattern, which better follows peak and trough concentrations of multiple-dose regimens. The main differences in these 3 models were that models 1 and 2 only include mean water use rates, but model 5 changes the water use rate on the basis of temperature variations from morning to night. As determined on the basis of LL, BIC, and AIC, model 5 had a slightly lower fit than either models 1 or 2. This model was included in subsequent comparisons because of the graphic fit and its consideration of an additional covariate. These 3 models were then compared on the basis of model calculated parameter estimates. The 3 models predicted parameters that were physiologically reasonable, although the Vd was slightly low on model 2 and close to the highest reported values for model 5 (**Table 1**).

Table 2—Parameter estimation of models 1, 2, and 5 for validation of ability to accurately simulate data independently collected by Dorr et al.[11]

Population parameter	Model 1 (150 μg/mL)	Model 2 (150 μg/mL)	Model 5 (150 μg/mL)
Volume per weight (mL/kg)	160	910	973
Kel (1/h)	0.278	0.278	0.279
Mean population water use rate	41.73	8.05	6.54
Concentration SD (μg/mL)	0.121	0.121	0.121

Water use data were not included for comparison because no water use data were directly measured.
See Table 1 for remainder of key.

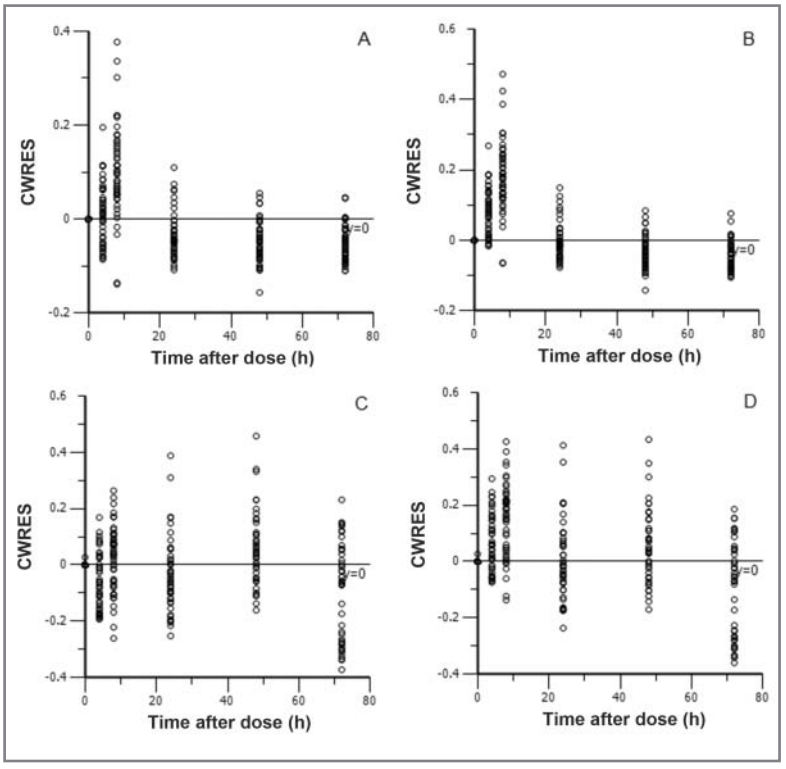

Figure 3—Conditional weighted residuals comparison for models 2 and 5 in a study modeling plasma concentrations of tetracycline in swine treated with tetracycline in water. Simulation set data are modeled by model 2 (A) and model 5 (B). The bottom panels show residuals for model 2 (C) and model 5 (D) for the validation data set (150 µg/mL). CWRES = Conditional weighted residuals.

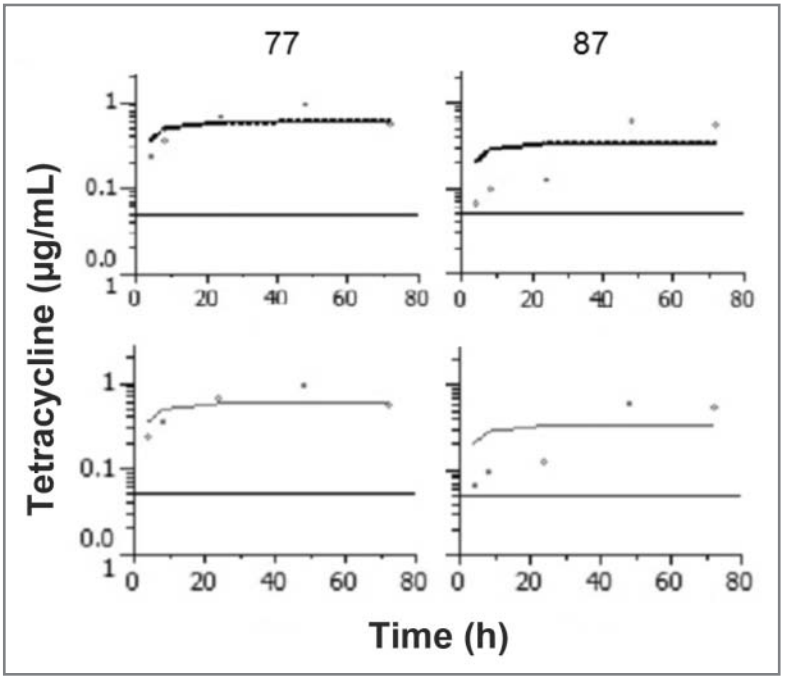

Figure 4—Predicted plasma concentration results for the validation data of 150 µg of tetracycline/mL in water in a study modeling plasma concentrations of tetracycline in swine treated with tetracycline in water. All graphs are on a semilogarithmic scale. Numerals 77 and 87 represent individual animals. The upper panel represents model estimations for model 2, and the lower panel represents model estimations for model 5. Data points are measured plasma concentration data. The solid line indicates predicted plasma concentration, and the horizontal line represents the lowest quantifiable concentration of tetracycline in plasma. Notice good fit of the data for animal 77 and poor fit of the data for animal 87.

The second stage of model selection observed the effect of the validation data set at 150 µg of tetracycline/mL administered in water to swine at 12 weeks of age. This data set was compared by use of the remaining 3 covariate models. The covariate model numbers with their parameter estimates were summarized (**Table 2**). The performance of these models revealed that model 1 had poor parameter estimates of mean population water use rate, which was caused by high variability and poor Vd that was outside of reported physiologic ranges for tetracycline hydrochloride. Model 1 was not considered a good estimator of the data in the validation data set.

The 2 best models (2 and 5) were then further compared for each of the populations. Representative graphic results of predicted plasma concentrations of the training data set for models 2 and 5 were obtained (**Figure 2**). Model 5 uses a water use rate that varies as a function of temperature, which generates a wave pattern as water use increases during the day and decreases at night. Plasma concentrations of tetracycline therefore peak toward the end of the day and are lowest in the early morning. In contrast, model 2 uses a constant daily water use rate; thus, no variability in plasma concentrations is seen during each 24-hour period. The conditional weighted residuals for the simulation and validation populations were determined (**Figure 3**). Both models revealed a bias in the water concentration at 8 hours for the simulation data set. For the validation data set, both models underestimated later time points and overestimated earlier time points, but neither model appeared vastly superior. The typical overestimation on later time points for both data sets may have been due to measuring plasma concentrations at trough sampling times. The weighted residual η values (parameter values) represented an approximately normal or log-normal distribution for model 5 data (not shown), whereas the η values for model 2 data (data not shown) were not distributed uniformly. Model 5 plasma concentration predictions for representative individual pigs from the validation data set (150 µg/mL) were determined (**Figure 4**). The 2 models were compared on the basis of their predictions of plasma tetracycline concentrations. It appeared that both models similarly fit the data for these animals. Subtle differences were found between the 2 models on the basis of estimated temperatures during winter, when pigs were kept within their thermoneutral zone. Finally, graphic simulations that used the data-selected parameter values were used to predict the simulation data (80 µg/mL) for an unknown population of animals (**Figure 5**). Subtle differences were again found be-

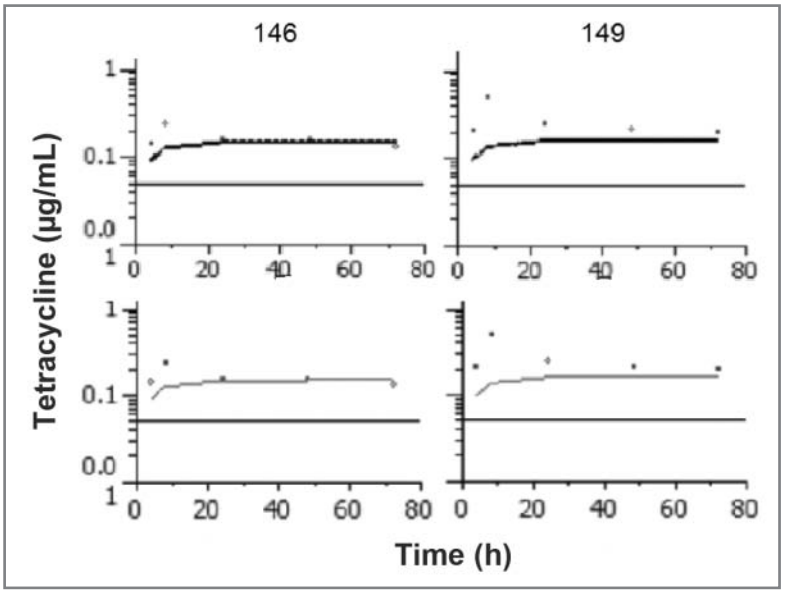

Figure 5—Predicted values of a simulation data set in a study modeling plasma concentrations of tetracycline in swine treated with tetracycline in water. The upper panel represents model estimations for model 2, and the lower panel represents model estimations for model 5. All graphs are on a semilogarithmic scale. Numerals 146 and 149 represent individual animals. Data points are actual plasma concentration data. The solid line represents predicted plasma concentration, and the horizontal line represents the limit of quantification of the assay for tetracycline. Notice good fit of the data for animal146 and poor fit of the data for animal 149.

tween the 2 models, but overall, both models appeared to simulate the data well. Model 5 often predicted slightly lower plasma concentrations than did model 2 because model 5 uses expected ambient temperatures to determine medication dose for the simulation data set.

Discussion

On the basis of the study of tetracycline administered in water by Mason et al,[2] there was an initial linear relationship between plasma concentration and the concentration of tetracycline in the water of pigs treated in commercial settings. This relationship is predicted by the following equation:

$$\text{Plasma concentration} = 0.0019 \times \text{water concentration} + 0.0435$$

This relationship had an R^2 value of approximately 0.79 for data from the Mason et al[2] study. The equation can also be applied to the Dorr et al[11] study, but it overestimates the mean plasma concentrations based solely on the tetracycline concentrations in the water. This overestimation is likely due to higher temperatures during the summer collection period for the Mason et al[2] study, whereas data were collected in the winter for the Dorr et al study.[11] From the limitations of this linear relationship, some other factors must be addressed to account for the variability seen among the individual animals and across the different populations of animals. The major differences in plasma concentrations of tetracycline from animals receiving the same treatment were not the apparent F or the elimination of the drug. The largest source of variability appeared to arise from water use and Vd.

In our modeling scheme, water use was responsible for most plasma concentration variability among animals. Mathematically, water use determines the dose of the medication that reaches the individual animal. The dose is then affected by the F and pharmacokinetic parameters of each pig. Some factors that greatly affect F are whether food is withheld from an animal and, if not, the amount of divalent cations in the food. In the other studies,[2,11] food was given ad libitum, which noticeably decreased the F of tetracycline. Divalent cation binding to tetracycline hydrochloride decreases its absorption across the intestinal wall and results in lower F. Despite the low F, the observed plasma concentration variability appeared to be most affected by the water use variable in our model. This parameter had a greater effect than any other parameter, except for Vd. For medications given with ad libitum dosing, typical pharmacokinetic programs cannot easily address the variability because they assume a known dosing schedule. Furthermore, the true dose each animal receives cannot be known or easily extrapolated.[23,29] Therefore, mean water use was approximated on the basis of water use of individual animals and then related back to physiology to help better explain what population-based water use would be expected for the validation data set. Unfortunately, the large variability in water use could not be explained just on the basis of a mean with an SD for a population of animals. Therefore, other factors were considered in the covariate models. The covariate that most affected water use was body weight. Other fixed effects or factors that affected the plasma concentrations were temperature and concentration of the medication in water.

Because data were only available from the original training data set, all model (2 and 5) results from the water consumption data will have an inherent similarity in dosing rates between the training and validation data sets because of model convergence on the initial parameter estimates. At this time, no relationship between the temperature and water use for grower-finisher pigs has been reported, but a relationship between temperature and water consumption has been reported for 150-kg sows[23] on the basis of the equation from Vandenheede and Nicks[30]:

$$I = 0.92T - 1.52$$

where I is water intake (L), T is temperature (°C), and 1.52 is the y-intercept for baseline water consumption. Data from the training set revealed high individual water use, which correlated well with the high ambient temperatures. On the basis of data from the Mason et al[2] study, water use was estimated by the following equation:

$$\text{Water use} = (\text{[temperature} - 20] + \text{constant}) \times \text{wt}$$

where temperature is in °C, wt is the body weight (kg), and constant is the drinking rate per hour within the thermoneutral zone (at 20°C) for a pig of that age (between 5 and 6.5 mL/kg/h for our study). With the

equation, almost equivalent values for estimated water consumption can be achieved for sows (body weight, 150 kg) when the low end of the thermoneutral zone temperature for sows is considered to be 10°C. Notably, the animals from the present study were growing and their water use was higher than a sow's would be given their higher metabolic rates and a higher concentration of body water[23] (Table 1).

The other covariate that greatly affected medication concentrations in the model was body weight. Body weight directly affected the apparent Vd and the total needed dose of tetracycline. Large variability was present in the model estimates of the Vd among animals of the different populations, perhaps in part due to age variability. The animals used to collect data for the training set were 8 weeks of age, whereas the other 2 sets of plasma concentration data came from animals that were 12 to 13 weeks of age. A wide range of Vd values (for the central compartment) has been reported for tetracycline (from < 1 to 4.5 L/kg).[16,17] Differences in the Vd may in part be affected by the percentage of plasma volume or total body water percentage on the basis of the animals' ages. Volumes of distribution in young animals may be higher than those in older animals because body water concentrations are higher in young animals and as animals age, body fat percentage increases.

The final sensitive model parameter was Ke. In the model, Ke ranged between 0.08 and 0.27 for the different data sets, which is related to the clearance rate by the Vd:

$$Cl = Ke \times Vd$$

where Cl is the clearance.

For tetracycline, most clearance occurs through the kidneys; therefore, we compared Ke across animals of the same age group. Clearance values reported by Kniffen et al[16] and Nielsen and Gyrd-Hansen[17] are 0.16 to 0.25 mL/kg/h as determined from ≥ 12-week-old pigs, whereas in the studies by Mason et al[2] and Mevius et al,[3] pigs were only 8 to 9 weeks old at the start of the study and had much lower clearances. Although this is only a 4-week difference at the start of the study, the clearance of young animals is often impaired up to 16 weeks of age in many domestic species that reach puberty at approximately 6 months of age.[31] Therefore, the body clearance for younger animals may in fact, as the model predicts, be lower than for the validation set of 12- to 13-week-old animals, which appeared to correspond to the literature clearance values of approximately 0.20 mL/kg/h.

When evaluating the models that fit the data best, it should be noted that model 2 did not include temperature as an effect on water use and model 5 used temperature to predict the water use. It appears that when more temperature data are available (ie, daily high and low ambient temperatures), model 5 could potentially be more useful than model 2, especially in predicting plasma concentrations at different times of the year. Model 5 also had less variability in the actual drinking rates than did model 2 across the different groups on a milligram per kilogram basis. Finally, the temperature changes seen during the study and described by model 5 mimicked the typical diurnal drinking pattern seen in pigs.

When the 2 chosen covariate models were compared, the simulation data set η appeared more skewed in model 2 than when temperature was controlled in model 5. Unfortunately, the validation data set did not contain temperature data; therefore, model 5 temperatures for data sets not containing temperature data were predicted on the basis of a likely thermoneutral range consistent with that time of year. Unfortunately, the true temperatures were unknown for all data collected by Dorr et al,[11] which prevented models 2 and 5 from being directly compared with the training set model. This potential model misspecification resulting from unknown temperatures may mask the temperature's true effect on the water consumption and consequently increase the apparent error between the model and the plasma concentrations among the 3 populations. The potential for model misspecification also applies to the Vd, which had the greatest variability in the models. Overall, the graphic simulations revealed that compared with the original linear relationship, variability of predicted plasma concentrations had improved greatly.

In the present study, the mixed-effects pharmacostatistical model related plasma tetracycline concentrations in 3 populations of pigs to individual pig water use and the tetracycline hydrochloride concentrations in the administered water. On the basis of the 2 best covariate models, water concentrations of medication and water use are 2 factors important in determining the plasma concentrations in swine exposed to medication in water. These factors appear to affect plasma concentrations most because elimination rates (Ke) and F have tight ranges for young swine of a uniform age range. These 2 models were able to accurately predict plasma concentrations for approximately 90% of the population. This type of modeling of plasma concentrations of tetracycline hydrochloride could be extended to populations of pigs that are being treated with other medications administered through water, such as florfenicol. The importance of these population-based models is to prevent the development of antimicrobial-resistant pathogens. Unfortunately, with older medications, such as tetracycline hydrochloride, reported bacterial MICs are high in relation to the attainable plasma concentrations.[2,28] Newer medications such as florfenicol still have reported MICs considerably less than achievable plasma concentrations.[32] The inclusion of this type of pharmacostatistical model when treating populations may help veterinary professionals and swine producers decrease the rate of development of antimicrobial-resistant pathogens. This model provides a way to compare population plasma concentrations in relation to MIC thresholds for bacteria. With a better understanding of how factors such as temperature and water concentrations affect ingested dose, producers and veterinarians may better use medications administered in water and better predict necessary changes in antimicrobial doses administered in water. This predictive approach to population treatment may decrease bacterial resistance to the chosen medication, especially when antimicrobial susceptibility testing finds MICs that are higher than typical for a specific bacterial pathogen. The water con-

centration and water use factors may also be considered in treating swine seasonally. It may appear valid to increase water concentrations of medications during the winter when lower ambient temperatures decrease drinking and there is a concurrent increase in the rate of respiratory infection transmission. Secondly, when factors are known that directly affect the medication concentrations in vivo, producers may be able to predict the effects of potential dosage miscalculations without expensive analytic testing of plasma samples from individual animals. From the findings of the present study, it can be stated that when F is known, water concentrations and water use are 2 major factors that explain the variability of plasma concentrations in animals treated with medicated water. Therefore, in selecting antimicrobials for use in water, ideal candidates should have high F in the treated species and be readily dissolvable in water, unlike tetracycline hydrochloride. If these 2 criteria are not met, then we predict that no matter how high the water use and water concentrations of the medication reach, plasma concentrations will remain low. As always, prudent discrimination in the initial antimicrobial selection should be performed prior to application of the criteria. These factors will need to be studied with other medications administered in water to verify our conclusions.

a. Phoenix WinNonMix NLME, version 1.73, Pharsight Corp, Mountain View, Calif.
b. 1-way ANOVA, SAS, version 9.1, SAS Institute Inc, Cary, NC.

References

1. Agerso H, Friis C, Haugegaard J. Water medication of a swine herd with amoxycillin. *J Vet Pharmacol Ther* 1998;21:199–202.
2. Mason SE, Baynes RE, Almond GW, et al. Pharmacology of tetracycline water medication in swine. *J Anim Sci* 2009;85:3179–3186.
3. Mevius DJ, Vellenga L, Breukink HJ, et al. Pharmacokinetics and renal clearance of oxytetracycline in piglets following intravenous and oral administration. *Vet Q* 1986;8:274–284.
4. Riviere JE. Basic principles and techniques of pharmacokinetic modeling. *J Zoo Wildl Med* 1997;28:3–19.
5. Martin-Jimenez T, Riviere JE. Population pharmacokinetics in veterinary medicine: potential use for therapeutic drug monitoring and prediction of tissue residues. *J Vet Pharmacol Ther* 1998;21:167–189.
6. del Castillo JR, Laroute V, Pommier P, et al. Interindividual variability in plasma concentrations after systemic exposure of swine to dietary doxycycline supplied with and without paracetamol: a population pharmacokinetic approach. *J Anim Sci* 2006;84:3155–3166.
7. Martin-Jimenez T, Riviere JE. Mixed effects modeling of the disposition of gentamicin across domestic animal species. *J Vet Pharmacol Ther* 2001;24:321–332.
8. Martín-Jiménez T, Riviere JE. Mixed-effects modeling of the interspecies pharmacokinetic scaling of oxytetracycline. *J Pharm Sci* 2002;91:331–341.
9. Peyrou M, Doucet MY, Vrins A, et al. Population pharmacokinetics of marbofloxacin in horses: preliminary analysis. *J Vet Pharmacol Ther* 2004;27:283–288.
10. Regnier A, Concordet D, Schneider M, et al. Population pharmacokinetics of marbofloxacin in aqueous humor after intravenous administration in dogs. *Am J Vet Res* 2003;64:889–893.
11. Dorr PM, Nemechek MS, Scheidt AB, et al. Water-flow variation and pharmacoepidemiology of tetracycline hydrochloride administration via drinking water in swine finishing farms. *J Am Vet Med Assoc* 2009;235:299–304.
12. Aarestrup FM. Veterinary drug usage and antimicrobial resistance in bacteria of animal origin. *Basic Clin Pharmacol Toxicol* 2005;96:271–281.
13. *WinNonLin user's guide*. Mountain View, Calif: Pharsight Corp, 2010;366–386.
14. Lindstrom ML, Bates DM. Nonlinear mixed effects models for repeated measures data. *Biometrics* 1990;46:673–687.
15. Yamaoka K, Tanaka H, Okumura K, et al. An analysis program MULTI(ELS) based on extended nonlinear least squares method for microcomputers. *J Pharmacobiodyn* 1986;9:161–173.
16. Kniffen TS, Bane DP, Hall WF, et al. Bioavailability, pharmacokinetics, and plasma concentration of tetracycline hydrochloride fed to swine. *Am J Vet Res* 1989;50:518–521.
17. Nielsen P, Gyrd-Hansen N. Bioavailability of oxytetracycline, tetracycline and chlortetracycline after oral administration to fed and fasted pigs. *J Vet Pharmacol Ther* 1996;19:305–311.
18. Martinez MN. Use of pharmacokinetics in veterinary medicine. Article II: volume, clearance, and half-life. *J Am Vet Med Assoc* 1998;213:1122–1127.
19. Williams PL. Structural identifiability of pharmacokinetic models—compartments and experimental design. *J Vet Pharmacol Ther* 1990;13:121–131.
20. Vonesh EF, Chinchilli VM, Pu K. Goodness-of-fit in generalized nonlinear mixed-effects models. *Biometrics* 1996;52:572–587.
21. Harvey RE. Observation of the drinking habits of weaned growing pigs in relation to the rationale of water medication. *Pig J* 1998;42:137–140.
22. Harvey RE. Water consumption in pigs. *Pig J* 1994;32:95–98.
23. Mroz Z, Jongbloed AW, Lenis NP, et al. Water in pig nutrition: physiology, allowances and environmental implications. *Nutr Res Rev* 1995;8:137–164.
24. Lee H, Ghosh SK. Performance of information criteria for spatial models. *J Stat Comput Simul* 2009;79:93–106.
25. Link WA, Barker RJ. Model weights and the foundations of multimodel inference. *Ecology* 2006;87:2626–2635.
26. Ludden TM, Beal SL, Sheiner LB. Comparison of the Akaike information criterion, the Schwarz criterion and the *F* test as guides to model selection. *J Pharmacokinet Biopharm* 1994;22:431–445.
27. Markon KE, Krueger RF. An empirical comparison of information-theoretic selection criteria for multivariate behavior genetic models. *Behav Genet* 2004;34:593–610.
28. Luthman J, Jacobsson SO, Bengtsson B, et al. Studies on the bioavailability of tetracycline chloride after oral administration to calves and pigs. *Zentralbl Veterinarmed A* 1989;36:261–268.
29. Xin H, DeShazer JA. Swine response to constant and modified diurnal cyclic temperatures. *Trans Am Soc Agric Eng* 1991;34:2533–2540.
30. Vandenheede M, Nicks B. Water requirements and drinking water for pigs. *Ann Med Vet* 1991:135:123–128.
31. Hardy RM, Osborne CA. Water deprivation test in the dog: maximal normal values. *J Am Vet Med Assoc* 1979;174:479–483.
32. Liu J, Fung KF, Chen Z, et al. Pharmacokinetics of florfenicol in healthy pigs and experimentally infected with *Actinobacillus pleuropneumoniae*. *Antimicrob Agents Chemother* 2003;47:820–823.

Appendix appears on the next page

Appendix

Model types and associated model selection criteria used in a study of tetracycline in swine treated with tetracycline in water.

Model	Model specification*	LL	AIC	BIC
1	drate = Mean drinking rate × exp(ndrate)	–286	588	616
2	drate = Mean drinking rate × Wt × exp(ndrate)	–284	584	612
3	drate = Mean drinking rate × teffect × exp(ndrate)	–310	635	664
4	drate = Mean drinking rate × Wt × teffect × exp(ndrate)	–489	993	1,022
5	drate = (teffect + mean drinking rate) × Wt × exp(ndrate)	–293	602	631

*Covariate model specifications for the pharmacokinetic model with associated selection criteria values for each of the 5 covariate forms.

drate = Mean population water use rate, calculated from known drinking rates. ndrate = Interindividual variability of the calculated mean population water use rate. teffect = Temperature – 20°C; to allow an additive drinking rate to the model instead of a multiplicative rate. Wt = Body weight.

All errors were exponential errors. An ambient temperature of 20°C represents the low end of the thermoneutral zone of early grower pigs.