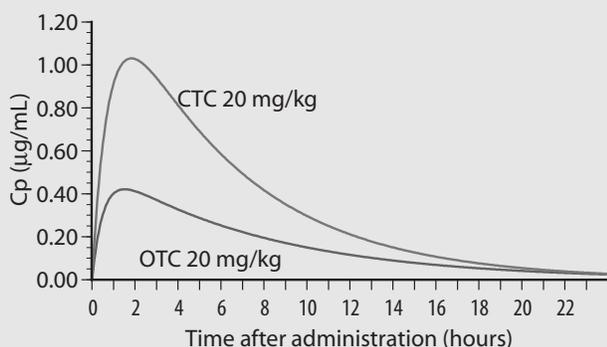


Figure 6



Simulated chlortetracycline (CTC) and oxytetracycline (OTC) plasma concentrations in pigs after administration of a 20 mg/kg bodyweight dose in feed

more quickly than OTC, as shown by the statistically significant difference in their respective k ($P = .033$). The elimination half-life ($t_{1/2}$) of CTC is thus 75% of OTC. Because CTC is absorbed more slowly and eliminated more quickly than OTC, the models predicted slightly greater daily variations in plasma concentrations of CTC compared to OTC (Figure 4).

Feeding behavior

Diurnal feeding patterns

Ad libitum feeding behavior of pigs induced a marked daily variation in both CTC and OTC plasma concentrations. In-feed dosages of both CTC and OTC differ between more-diurnal pigs and less-diurnal pigs when a targeted plasma drug concentration is required (Table 5). Because 40-kg (88-lb) pigs consume about 70% of their daily meals during the daytime,⁸ the model should predict that the drug accumulated in the body during the day and was eliminated during the night. The model did predict that drug plasma concentrations were lowest by the beginning of the diurnal period (approximately 7:00 a.m.), and highest at its end (7:00 p.m.) (Figure 4).

Pig numbers in pen

The number of pigs in the pen (holding pen density constant) did not prove to be a significant factor in determining plasma drug concentration over time (data not shown).

Model validation

In general, our model generated predictions that were consistent with the literature (Figures 7–8). The model for OTC was in slightly better agreement with reported plasma concentrations (Figure 7) than was the model for CTC (Figure 8).

Summarizing equation

The simulations were used to devise an equation where the drug dosage to be given to pigs is calculated by the antibiotic concentration in plasma, the daily feed intake of pigs, as well

as their feeding behavior, in the nonlinear equation:

$$D_{CTC} = 69 \times TPL - 35 \times e^{DFIR} + 18 \times e^{DDMR} \quad (\text{Equation 5})$$

$$D_{OTC} = 141 \times TPL - 62 \times e^{DFIR} + 32 \times e^{DDMR} \quad (\text{Equation 6})$$

Where:

- D_{CTC} and D_{OTC} are the dosage concentrations of OTC and CTC (in mg per kg bodyweight) to be administered in feed to pigs achieve the targeted plasma concentration TPL (in μg per mL),
- $DFIR$ is daily feed intake of pigs, which is represented as a BW ratio (i.e., if the amount of feed ingested daily is equivalent to 4% of BW, then a value of 0.04 is given to $DFIR$), and
- $DDMR$ is the ratio of daily meals eaten during the day by the pigs (i.e., if pigs eat nine of their 12 daily meals during the day, then $DDMR$ has a value of 0.75).

Discussion

Model validation

The plasma concentrations of OTC and CTC predicted by our models were in close agreement with those reported by Asanuma, et al.,¹⁷ Mevius, et al.,²³ and Hunneman, et al.,²⁶ strongly indicating that our model is valid. Moreover, the models made surprisingly accurate predictions for CTC and OTC plasma concentrations given by the 7-day use of medicated drinking water.²⁴ However, the latter findings are not adequate to support the application of the models to administration of medicated water.

As expected, these models were not able to predict plasma concentrations of OTC in fasted piglets dosed with a medicated drench.^{22,23} Plasma OTC concentrations found with medicated drench administration to fasted^{22,23} or fed²² pigs were considerably higher than both concentrations predicted with the equations and those from their experiments using medicated feeds.^{25,26} Intestinal absorption of OTC is reduced by the presence of food.⁵

Our model for CTC was also in close agreement to observations reported by Andrews, et al.¹⁸ in pigs that were challenged with *Pas*-

Table 5

Dosages of CTC and OTC (in mg/kg bodyweight) to be given in feed to provide selected targeted plasma concentrations for 20 hours per day in pigs weighing 40 kg with a daily feed intake equivalent to 4% of their body weight, and distinct diurnal feeding behaviors

Targeted plasma concentration ($\mu\text{g/mL}$)	Drug type:		OTC	
	CTC	CTC	65%	85%
	% of meals eaten during the day:		Dose required (mg/kg bodyweight)	
0.10	65%	85%	11	21
0.25	65%	85%	32	42
0.50	65%	85%	67	77
0.75	65%	85%	103	112
1.00	65%	85%	138	148