

Water-flow variation and pharmacoepidemiology of tetracycline hydrochloride administration via drinking water in swine finishing farms

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Objective—To evaluate variation of drinking-water flow rates in swine finishing barns and the relationship between drinker flow rate and plasma tetracycline concentrations in pigs housed in different pens.

Design—Cross-sectional (phase 1) and cohort (phase 2) studies.

Sample Population—13 swine finishing farms (100 barns with 7,122 drinkers) in phase 1 and 100 finishing-stage pigs on 2 finishing farms (1 barn/farm) in phase 2.

Procedures—In phase 1, farms were evaluated for water-flow variation, taking into account the following variables: position of drinkers within the barn, type of drinker (swing or mounted), pig medication status, existence of designated sick pen, and existence of leakage from the waterline. In phase 2, blood samples were collected from 50 pigs/barn (40 healthy and 10 sick pigs) in 2 farms at 0, 4, 8, 24, 48, and 72 hours after initiation of water-administered tetracycline HCl (estimated dosage, 22 mg/kg [10 mg/lb]). Plasma tetracycline concentrations were measured via ultraperformance liquid chromatography.

Results—Mean farm drinker flow rates ranged from 1.44 to 2.77 L/min. Significant differences in flow rates existed according to drinker type and whether tetracycline was included in the water. Mean drinker flow rates and plasma tetracycline concentrations were significantly different between the 2 farms but were not different between healthy and sick pigs. The plasma tetracycline concentrations were typically < 0.3 µg/mL.

Conclusions and Clinical Relevance—Many factors affected drinker flow rates and therefore the amount of medication pigs might have received. Medication of pigs with tetracycline through water as performed in this study had questionable therapeutic value. (*J Am Vet Med Assoc* 2009;235:299–304)

Injectable antimicrobials are used to treat individual pigs with bacterial infections. However, with large herd sizes, labor constraints, and the ability of some pathogens to spread quickly within a herd, swine producers must rely on other therapeutic approaches to treat groups of pigs, and oral administration of antimicrobials through drinking water is a common strategy. Medication of drinking water minimizes labor requirements and can be used to metaphylactically treat large groups of pigs. Farm personnel prefer to use medicated drinking water because of the relative ease of administration and safety (eg, avoidance of broken needles in the bodies of pigs), compared with injectable antimicrobials.

The degree of absorption of various orally administered antimicrobials is highly variable. In animals, the gastrointestinal system readily absorbs some antimicrobials such as tiamulin, and substantial blood concentra-

ABBREVIATION	
UPLC	Ultraperformance liquid chromatography

tions are achieved within a few hours.¹ In contrast, other antimicrobials such as spectinomycin and neomycin are poorly absorbed. The tetracyclines (oxytetracycline, tetracycline, and chlortetracycline) are widely used to medicate drinking water; however, in grower-finisher pigs, the bioavailability or amount of active compound that enters circulation is lower after oral administration than after IV administration.^{2,3} In pigs, IV or IM administration of antimicrobials yields greater, more rapid increases in blood concentrations of antimicrobials than does medication of drinking water.³

Mass treatment of pigs in integrated swine production systems requires the administration of medi-

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cations through waterlines; however, several potential problems are associated with this treatment strategy.⁴ For example, drinking-water flow rates can vary when lines are clogged (eg, with residues from other treatments or sludge) or when water pressure increases or decreases. The palatability of water can also decrease when medications are added, affecting the likelihood that pigs will consume the water. In addition, whereas healthy pigs may receive the intended dosage, it is not known whether clinically ill pigs consume sufficient water to receive the same dosage. However, a study⁵ in which pigs were experimentally infected with *Actinobacillus pleuropneumoniae* revealed that pigs drink less water when infected.

The purpose of the study reported here was to evaluate water flow rates from drinkers (water nipples) in several commercial finishing pig facilities and then assess plasma tetracycline concentrations in finishing pigs after administration of tetracycline HCl via drinking water. The primary objectives were to determine the relationship between drinker flow rate and plasma tetracycline concentrations in finishing-stage pigs housed in different pens and to determine whether plasma tetracycline concentrations differed between healthy and clinically ill pigs.

Materials and Methods

Animals and farms—To measure drinking-water flow rates in phase 1 of the study, a convenience sample of 13 swine finishing farms was enrolled. All finishing farms were managed by 1 company, and each had the same genetic lines of pigs (mixed breed). One hundred barns were included, with each farm containing between 5 and 9 barns. Each barn contained between 32 and 44 pens. Approximately 22 to 23 pigs were housed in each pen.

To determine plasma tetracycline concentrations in pigs in phase 2 of the study, 2 of the 13 finishing farms were selected on the basis of differences in drinker flow rates as determined in phase 1. One farm (farm 3) had a low and uniform drinker flow rate (mean \pm SEM rate, 1.44 ± 0.65 L/min). In contrast, the second farm (farm 5) had a high and variable flow rate (2.63 ± 1.17 L/min). On these farms, 2 barns (1 barn/farm) were chosen as test barns on the basis of the age of the pigs (same age between the 2 test barns) and the lack of previous medicated water administration. In each test barn, 10 pigs were selected (convenience sample from the first 10 pigs in the pen to be caught and tested) from the designated sick pen and 4 additional pens (1 pen/barn zone for a total of 50 pigs/barn) and ears were tagged for identification. Pigs in the sick pen had various signs of disease including lameness, unthrifty appearance, wasting, and respiratory problems. The barns within the 2 farms were of the same type of construction, were under the same management, and had the same number of pens ($n = 36$), stocking density (22 to 23 pigs/pen), drinker type (swing), and age of pigs (11 to 12 weeks). This study protocol adhered to the Institutional Animal Care and Use Guidelines of North Carolina State University.

Determination of drinker flow rates—In 6 of the farms in phase 1 of the study, nipple drinkers^a were mounted on each side of the pen dividers (2 drinkers/pen). On the other 7 farms, swing-type drinkers with 2 nipples^b/drinker line were used. For the purpose of the study, each barn was divided into blocks to create 4 zones with pen numbers identically assigned by position within the barn (Figure 1). During the evaluation of drinker flow rates, water medication (typically tetracycline) was being used in at least 1 barn/farm. Consequently, 1,036 drinkers were assessed (from a total of 7,122 drinkers) while medication was used. The waterlines originated at the front of the barn, and consequently, it was assumed that water pressure and flow rates would be greater in pens at the front of the barn than in pens near the rear of the barn. The drinker flow rates (L/min) were determined by measurement of free-flow water with a graduated cylinder. Flow rates were quantified for all drinkers and are expressed as mean \pm SEM unless otherwise indicated.

Medication of water with tetracycline HCl—For phase 2 of the study, tetracycline HCl soluble powder^c was diluted in a stock solution for administration through a medicator (1:128).^d According to the manufacturer's instructions for the tetracycline product, the stock solution (34 mg/mL) was diluted with drinking water to provide 260 μ g of tetracycline/mL of water.

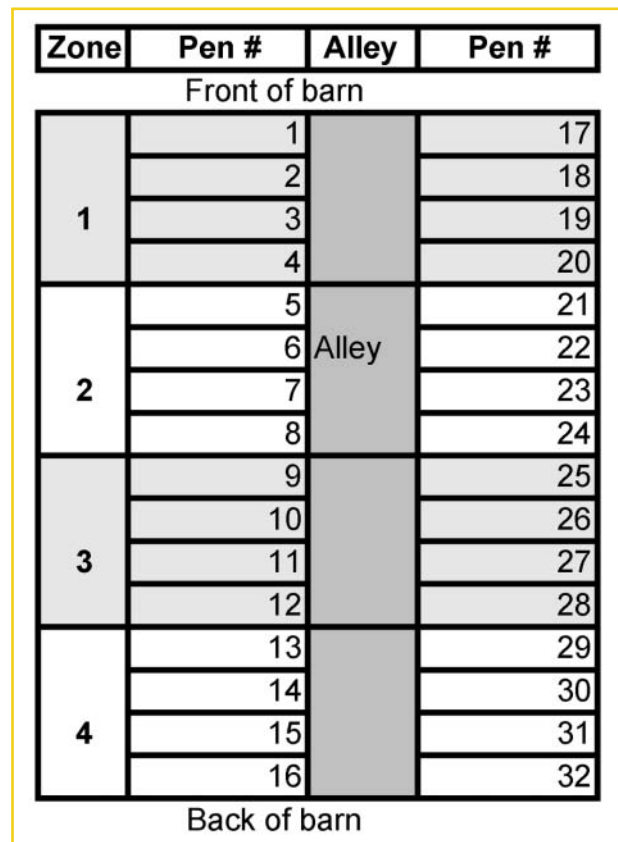


Figure 1—Designation of zones and pens for swine finishing barns in a study to evaluate water flow rate in drinkers.

Estimates of water use and drinker flow rates were used to set the medicator to deliver tetracycline HCl at a dosage of 22 mg/kg (10 mg/lb) in the test pens. The medicated water was provided to the pigs for 3 days, and water flow rates were determined daily for each drinker in the pens.

Collection of blood and water samples—Blood samples were collected from between the anterior vena cava and a caudal jugular vein in pigs from test pens prior to medication (0 hours) and at 4, 8, 24, 48, and 72 hours after the administration of medicated water began. Water samples were collected from the drinkers at the same points. Blood samples were centrifuged, and the plasma was harvested and stored at -80°C until analyzed.

Measurement of plasma tetracycline concentration—Plasma tetracycline concentrations were measured by means of UPLC in accordance with an established protocol.⁶ A 200- μL aliquot of thawed plasma (or water) was added to a centrifugal filter device^c containing a regenerated cellulose membrane^f along with 200 μL of releasing agent (78% water, 20% acetonitrile, and 2% phosphoric acid). The device was then agitated with a vortex machine for 5 seconds and centrifuged for 30 minutes at $8,500 \times g$. The filtrate was transferred to a sample vial.

Ultraperformance liquid chromatography was performed by use of an automated UPLC system^g with a tunable UV detector^h and a mass spectrometer.ⁱ The mobile phase was composed of a mixture of water and acetonitrile (80:20), with 0.2% acetic acid added to both the water and acetonitrile. Samples were maintained at 4°C , and the column^j (particle size, 1.7 μm ; column size, $2.1 \times 50 \text{ mm}$) was maintained at 40°C during analysis. An injection volume of 2 μL was used. The molecular ion of tetracycline (mass-to-charge ratio, 445; positive electrospray mode) was used in tetracycline quantification, whereas the tunable UV detector set at 355 nm was used for confirmation of the results.

For the standard curve, standards were prepared by adding tetracycline HCl^k (> 95%) to porcine plasma and freezing. These known standards (0, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, and 10.0 μg of tetracycline/mL) and a blank consisting of unadulterated porcine plasma were then prepared in a manner similar to the study plasma samples and used to determine the slope and linearity of the standard curve. In standard curves for UPLC analyses, the x-axis represents the compound concentration and the y-axis represents area under the curve. Tetracycline concentrations were subsequently extrapolated from the standard curve. The R^2 values for all analyses were > 0.99 , whereas the linear range was between 0.05 and 10 $\mu\text{g}/\text{mL}$ (80% to 120% recovery). The limit of quantification was 0.05 $\mu\text{g}/\text{mL}$, and the limit of detection was 0.01 $\mu\text{g}/\text{mL}$ (a peak was consistently evident; however, recoveries for 0.05 $\mu\text{g}/\text{mL}$ were outside an acceptable range to be quantified). Similar procedures were used to evaluate tetracycline concentrations in samples of water collected from the drinkers.

Statistical analysis—For the drinker flow rates in phase 1 of the study, an ANOVA was performed by use of commercial software^l to assess the associations between drinker flow rate and medication (yes or no), drinker type, pen, and farm. Interactions evaluated included those between the variables medication and drinker type, medication and pen, and drinker and pen and among the variables medication, drinker type, and pen. Means were compared with the Tukey test.

In phase 2 of the study, the actual initiation of water consumption by each pig could not be controlled, so for statistical purposes, 0 hours was defined as the point at which the medicator was turned on in the barn. In addition, the frequency of sample collection was inadequate to provide sufficient data to accurately evaluate pharmacokinetic parameters such as steady-state volume of distribution. Therefore, an ANOVA was used to evaluate the association between tetracycline concentration and farm, pen, time of blood sample collection, all 2-way interactions between these variables, and the interaction among farm, pen, and time. Means were compared by use of the Tukey test. Because drinker flow rates were measured for each pen, pen served as the term for drinker flow rate within the ANOVA and the comparison of mean plasma tetracycline concentrations for pens served to assess the influence of drinker flow rate on plasma tetracycline concentration.

Results

Drinker flow rates—Results of the final ANOVA model indicated that drinker type and tetracycline medication of water were significantly ($P < 0.01$) associated with the drinking-water flow rate in the 13 farms enrolled in phase 1 of the study. These flow rates varied among farms and barns (Table 1 and Figure 2). Mean drinker flow rates among the 13 test sites ranged from 1.44 to 2.77 L/min. Variation in flow rates was evident among barns, and the pen-to-pen variation

Table 1—Mean \pm SEM water flow rates (L/min) for drinkers that were mounted on pen dividers (1 to 2 drinkers/pen) or were swing-type drinkers (2 nipples/drinker) in 13 swine finishing farms.

Farm	Drinker type	No. of barns evaluated*	No. of drinkers evaluated	Water flow rate (L/min)
1	Mounted	8	672	2.33 ± 0.04
2	Swing	5	440	2.37 ± 0.06
3†	Swing	9	648	1.44 ± 0.02
4	Swing	9	648	1.85 ± 0.03
5†	Swing	9	648	2.63 ± 0.05
6	Mounted	6	424	2.32 ± 0.07
7	Swing	9	704	2.48 ± 0.03
8	Mounted	8	272	2.58 ± 0.04
9	Swing	9	648	2.06 ± 0.04
10	Mounted	8	702	2.20 ± 0.04
11	Swing	7	560	2.20 ± 0.04
12	Mounted	7	504	2.77 ± 0.05
13	Swing	7	252	2.62 ± 0.06

*The number of pens in each barn ranged from 36 to 44. †Farms that participated in phase 2 of the study to determine plasma tetracycline concentrations in pigs that received medicated water through drinkers.

within barns was high (Figure 3). The flow rates did not differ throughout the length of the barns.

The mean drinker flow rate was significantly less from drinkers delivering medicated water ($1.96 \pm$

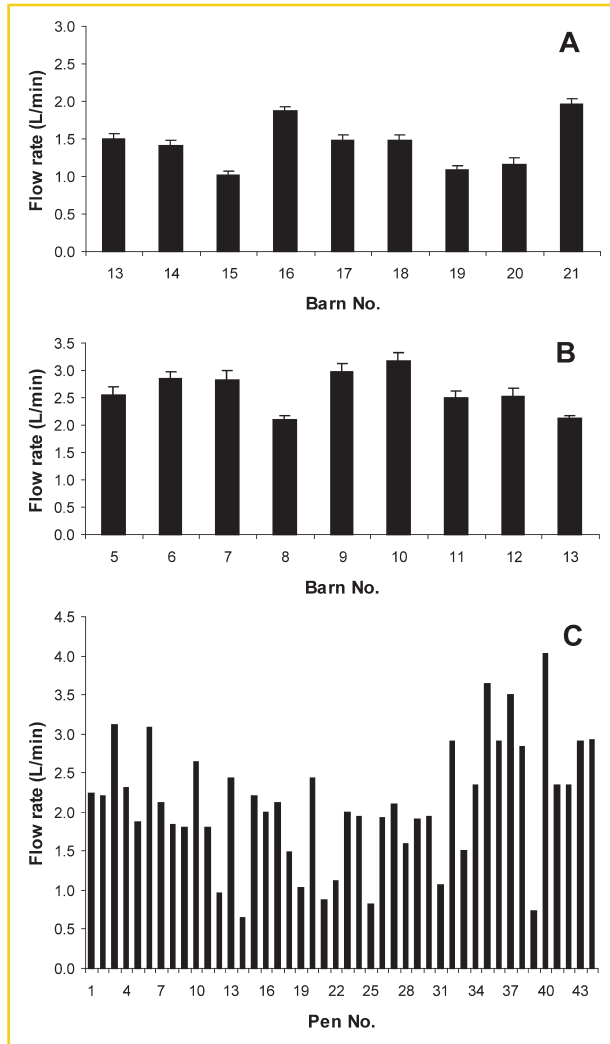


Figure 2—Mean \pm SEM water flow rates from drinkers in 2 representative swine finishing farms (A and B) and a representative finishing barn (C), revealing the variation among barns and pens.

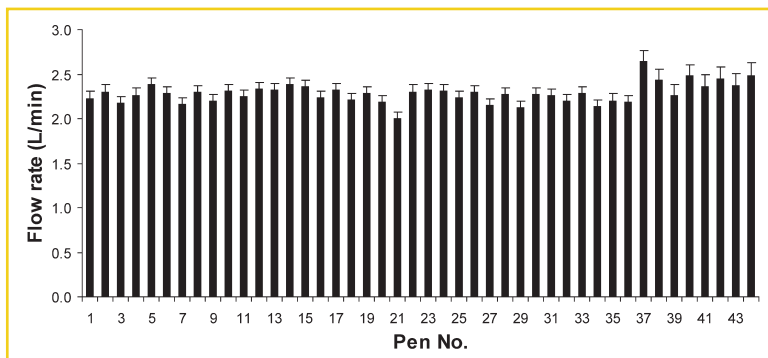


Figure 3—Mean \pm SEM water flow rates by pen for drinkers on 13 farms ($n = 100$ barns). Pen number was assigned identically within each barn according to pen position and, therefore, proximity of the pen and its drinkers to the origin of the water.

0.03 L/min) than from drinkers without medication (2.3 ± 0.01 L/min). Drinker flow rates also differed significantly between drinker types. Swing drinkers ($n = 4,584$) provided 2.17 ± 0.02 L/min, whereas the mounted drinkers (2,538) provided 2.43 ± 0.02 L/min. A significant interaction was detected between drinker type and administration of medication. Mounted drinkers that were not used to administer tetracycline had a significantly higher flow rate (2.71 L/min) than those that were used to administer tetracycline (2.39 L/min). Regardless of whether water contained tetracycline, the mounted drinkers had significantly higher flow rates than swing drinkers that did (1.76 L/min) or did not (1.83 L/min) provide medicated water. The difference between mean drinker flow rates in swing drinkers that did or did not provide medicated water was not significant.

Plasma tetracycline concentrations—When building the ANOVA model to identify factors associated with drinker flow rate in phase 2 of the study, the variable pen was identified as not significant ($P = 0.76$); consequently, that variable and the associated interaction terms were removed from the model. The final ANOVA model included the variables medication, drinker type, interaction between medication and drinker type, and farm, which served as the error term.

Drinker flow rates were greater ($P < 0.01$) in the test barn of farm 5 (3.90 ± 0.04 L/min) than in the test barn of farm 3 (1.40 ± 0.03 L/min). Plasma tetracycline concentrations increased from 0 hours to reach peak concentrations at 8 hours in farm 3 and at 8 hours and 48 hours in farm 5 (Figure 4). A secondary peak in farm 5 was attributed to plasma tetracycline concentrations in 2 of the 5 pens (Figure 5). Plasma tetracycline concentrations did not differ between pigs from sick or healthy pens. In each farm, 2 pigs in the sick pens died before the completion of the study. Tetracycline was not detected in the plasma of these particular pigs before death, thereby indicating that these pigs likely failed to consume water.

Overall, the mean plasma tetracycline concentration after administration of medicated drinking water began was greater in pigs from farm 5 (0.27 ± 0.01 $\mu\text{g/mL}$) than in those from farm 3 (0.16 ± 0.01 $\mu\text{g/mL}$). Regardless of this difference, considerable variation was evident in plasma tetracycline concentrations among individual pigs. The largest values of plasma tetracycline concentration (0.96 and 0.56 $\mu\text{g/mL}$) were obtained from 1 pig from farm 5 and 1 pig from farm 3, respectively.

The tetracycline concentration in drinking water, when assessed at the level of drinkers, was an additional factor that influenced plasma tetracycline concentration. The UPLC analysis revealed that tetracycline concentrations in drinking water were 85.03 ± 2.10 $\mu\text{g/mL}$ and 153.10 ± 7.40 $\mu\text{g/mL}$ for farms 3 and 5, respectively. Therefore, the pigs in the test barn

of farm 5 had access to greater drinker flow rates and higher water concentrations of tetracycline than did the pigs in the test barn of farm 3.

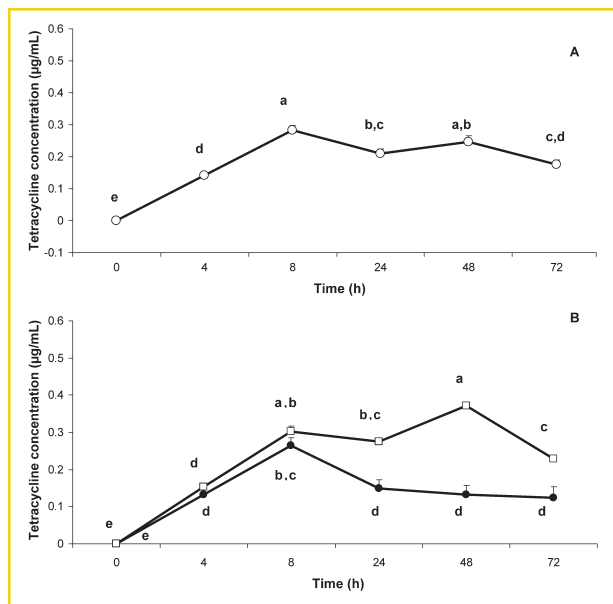


Figure 4—Mean \pm SEM plasma tetracycline concentrations in pigs (12 weeks of age; 10 pigs/pen; and 5 pens/barn) treated with tetracycline HCl administered via drinking water for all pigs and all pens in 1 barn from each of 2 farms (A) and by farm (farm 3, circles; farm 5, squares). Datum points with different letters are significantly ($P < 0.05$) different.

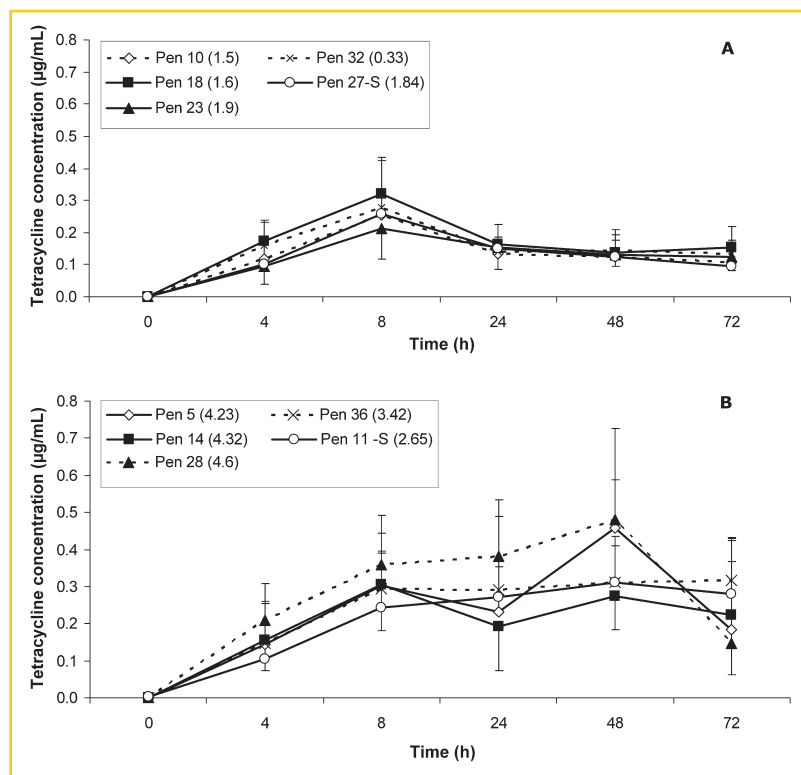


Figure 5—Mean \pm SD plasma tetracycline concentrations in pigs (12 weeks of age; 10 pigs/pen) treated with tetracycline HCl via drinking water in different pens in 1 barn from each of farm 3 (A) and farm 5 (B). Values in parentheses represent drinker flow rates (L/min). Sick pens are identified with an S after the pen number. The barn from farm 5 had a significantly ($P < 0.05$) greater drinker flow rate than the barn from farm 3.

Discussion

When data from other reports^{7,m} were taken into consideration, we estimated that the pigs in the present study likely consumed between 2 and 3 L of water each day during the study. This meant that with a tetracycline concentration of 153 $\mu\text{g/mL}$ of drinking water, the pigs in farm 5 would have received 306 to 450 mg of tetracycline/pig/d. In contrast, pigs in farm 3 would have received ≤ 255 mg of tetracycline/pig/d. Although these dosages of tetracycline may be suboptimal, in another study,⁸ provision of tetracycline HCl at 400 and 800 mg/L in drinking water resulted in serum tetracycline concentrations of < 0.6 $\mu\text{g/mL}$ (by 60 hours after administration began) and 0.8 $\mu\text{g/mL}$ (10 hours after administration began), respectively. In that study, administration of tetracycline at 40 mg/kg in 200 mL of drinking water resulted in serum concentrations of < 1 $\mu\text{g/mL}$ in calves and pigs from which food was not withheld. Results of the present study confirmed those of other studies^{3,9} in which medication of drinking water yielded inconsistent and low plasma tetracycline concentrations in recipients.

The finding of low plasma tetracycline concentrations in pigs that consumed medicated drinking water raises concern about absorption of the antimicrobial. Feed interferes with absorption because pigs and calves from which food has been withheld have higher plasma tetracycline concentrations when receiving tetracycline via drinking water than do pigs and calves with unrestricted food intake.⁸ In other studies involving pigs, ingestion of drinking water medicated with doxycycline (90 $\mu\text{g/mL}$ of drinking water) resulted in mean plasma doxycycline concentrations ranging from 0.83 to 0.96 $\mu\text{g/mL}$ ¹⁰ to 1.37 \pm 1.2 $\mu\text{g/mL}$.¹¹ Despite marked differences among pigs in those studies, these plasma doxycycline concentrations were higher than the minimum inhibitory concentrations of doxycycline reported for bacterial pathogens of the porcine respiratory tract.¹¹ Evidently, absorption of doxycycline is sufficient at the aforementioned concentrations, at least in controlled experimental conditions, to yield therapeutic plasma doxycycline concentrations in pigs.

Perhaps the most critical question is whether the plasma tetracycline concentration achieved via administration of tetracycline in drinking water is sufficient to be of therapeutic value. The minimum inhibitory concentrations of various antimicrobials including tetracycline have been determined for several bacterial pathogens of swine, including *A pleuropneumoniae*, *Pasteurella multocida*, *Salmonella Cholerasuis*, *Salmonella Typhimurium*, and *Streptococcus suis*.¹² For most of these organisms, the minimum inhibitory concentrations ranged from 0.13 to > 32 μg of tetracycline/mL and the 90% inhibitory concentrations were typically ≥ 32 μg of tetracycline/mL.

Because most plasma tetracycline concentrations were $< 0.3 \mu\text{g/mL}$ in pigs in the present study, medication of drinking water with tetracycline as performed would have questionable therapeutic value.

The results of our study indicated that drinking-water flow rates varied among farms, barns within farms, and pens within barns and also varied according to type of drinker and whether tetracycline was added to the water. A major problem was identified in the inconsistent drinker flow rates among individual drinkers, irrespective of the overall flow rate within a barn. With these types of variation, it is difficult to achieve uniformity of antimicrobial ingestion by pigs. This lack of uniformity was evident in the variation in plasma tetracycline concentrations. For both test barns, it is likely that poor antimicrobial solubility, malfunctioning medicators, sludge in the waterlines, or any of the aforementioned potential water delivery system problems contributed to the modest tetracycline concentrations in the water. Although the antimicrobial concentrations were the same in water samples from the drinkers in different pens within farms, plasma tetracycline concentrations varied among pigs from those farms. Drinker flow rate may have contributed to the variation in plasma tetracycline concentrations; however, it was evident that the pigs ingested differing quantities of antimicrobial during the 72-hour study period. This difference likely reflected variable water ingestion by pigs. Most importantly, water tetracycline concentrations were considerably less than those recommended by the manufacturer of the tetracycline product; consequently, it was not surprising that plasma tetracycline concentrations were also lower than anticipated.

Collectively, variation in drinker flow rates and problems associated with dilution and delivery of antimicrobials create an important challenge for swine producers and farm personnel. The findings of the study reported here raise serious concerns regarding the effectiveness of medications, particularly tetracycline, administered via drinking water for treatment of pigs.

- a. Trojan Model 75 Nipple, Trojan Specialty Products, Dodge City, Kan.
- b. Trojan Waterswing, Trojan Specialty Products, Dodge City, Kan.
- c. AmTech Tetracycline Hydrochloride Soluble Powder-324, Teva Animal Health, St Joseph, Mo.

- d. HN55 Fixed Rate Injector, Chemilizer, Largo, Fla.
- e. Micron centrifugal filter unit, Millipore, Billerica, Mass.
- f. Ultracel YM-10 (10,000 molecular weight cutoff), Millipore, Billerica, Mass.
- g. ACQUITY UPLC system, Waters Corp, Milford, Mass.
- h. Waters Corp, Milford, Mass.
- i. EMD 1000 mass spectrometer, Waters Corp, Milford, Mass.
- j. ACQUITY UPLC bridged-ethyl hybrid C_8 column, Waters Corp, Milford, Mass.
- k. Fluka BioChemika, Buchs, Switzerland.
- l. Statistix, Version 9, Analytical Software, Tallahassee, Fla.
- m. Mroz Z, Jongbloed AW, Van Diepen JTM, et al. Excretory and physiological consequences of reducing water supply to non-pregnant sows (abstr). *J Anim Sci* 1995;73(suppl 1):213.

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