FARAD Digest

Effect of formulation and route of administration on tissue residues and withdrawal times

Butch KuKanich, DVM, PhD, DACVCP; Ronette Gehring, BVSc, MMedVet; Alistair I. Webb, BVSc, PhD, DACVA; Arthur L. Craigmill, PhD, DABT; Jim E. Riviere, DVM, PhD

The formulation of a drug can have profound effects on tissue residues and, consequently, **withdrawal times (WDTs)** in food animal species. The WDT is the time after completion of treatment needed for tissue concentrations of the drug and any metabolites to decrease to less than the tolerance value or drug concentrations considered safe for human consumption. A drug can have a zero WDT if, after administration, the concentrations in the tissues are less than the tolerance value. A more thorough review of WDTs and tolerances and how they are determined has been published.[1]

The terminal half-life is the pharmacokinetic term that indicates the time for concentration of the drug to decrease by 50%. The terminal half-life is often related to the rate of drug elimination, but in certain circumstances, when the rate of absorption after extravascular administration is much slower than the rate of elimination, the terminal half-life is determined by the absorption, a condition termed the flip-flop phenomenon (**Figure 1**). The flip-flop phenomenon can occur because of inherent physiochemical properties of the drug or modification of the dosage form (eg, slow-release formulations) or by complexing of the drug with another component that must be removed prior to absorption. The strategy of such a formulation is to increase the time between doses (the administration interval), but such formulations can result in subtherapeutic concentrations and prolonged residues that require a prolonged WDT.[2]

Common Causes of Illegal Residues

The most common causes of illegal residues are failure to adhere to recommended WDTs, poor record keeping, and inadvertent administration of the wrong drug or dose.[3] Animals should be uniquely identified so a treated animal will not be slaughtered or milked prior to the proper WDT. The dose, length, route, and site of administration; formulation; and person administering the medication should be recorded to identify the causes of residues, should they occur. Additionally, it is important to ensure that the correct medication is administered because many labels and bottles look similar.

Administration of inappropriate formulations can have profound effects on the WDT of a drug and lead to illegal tissue residues. For example, conventional formulations of oxytetracycline typically have a labeled WDT of 18 to 19 days, whereas long-acting formulations have a 28-day WDT. Benzathine penicillin has a labeled WDT of 30 days, whereas for procaine penicillin, the WDT is 10 days.

Extralabel routes of drug administration can be a cause of illegal tissue residues. **Procaine penicillin G (PPG)** should be administered IM, not SC. Subcutaneous injection of procaine penicillin leads to hematoma formation, inflammation, and scar tissue that cause delayed and incomplete absorption.[4] Delayed drug absorption can also occur if a drug is administered into a fascial plane where there is poor

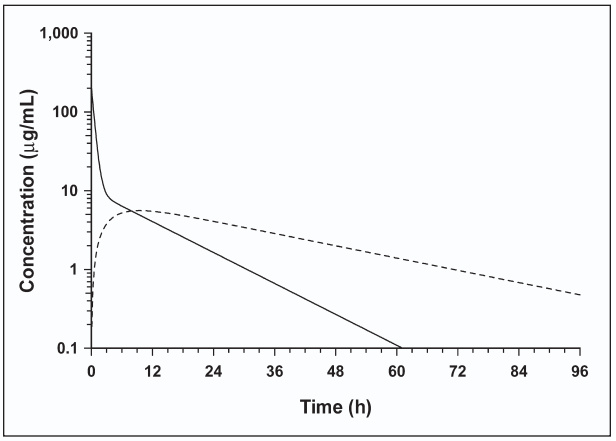

Figure 1—Expected plasma profile for long-acting oxytetracycline (20 mg/kg [9.1 mg/lb]) in cattle after IV (—) and IM (- - -) administration, revealing the flip-flop phenomenon. The terminal half-lives after IV and IM administration are 9 and 23 hours, respectively, despite administration of the same formulation.

From the Food Animal Residue Avoidance Databank (FARAD), Department of Biomedical Sciences (KuKanich), and Center for Chemical Toxicology Research and Pharmacokinetics (Gehring, Riviere), College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606; Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Webb); and the Department of Environmental Toxicology, College of Agriculture and Environmental Sciences, University of California, Davis, CA 95616 (Craigmill). Dr. KuKanich's present address is Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506-5802.
Supported by the USDA.
Address correspondence to Dr. KuKanich.

blood supply. Intramuscular injection of flunixin causes tissue damage, inflammation, and delayed and incomplete absorption, which can result in illegal residues.[5–7]

Drug selection can also lead to prolonged tissue residues. Administration of a long-acting drug formulation to a dehydrated, hypotensive animal or one with endotoxemia can result in delayed and incomplete drug absorption that leads to therapeutic failure, illegal residues, or both.

Some drugs (or dosages) are labeled to be administered for a single injection only. A long terminal half-life may result in tissue drug concentrations that are less than the tolerance value after administration of a single dose, but administration of a second dose can result in an unexpected increase in the time for concentrations to decrease to less than the tolerance value, which results in "stacking" (**Figure 2**).[8] Examples of this include multiple administrations of the long-acting oxytetracycline formulation (20 mg/kg [9.1 mg/lb]) or florfenicol (40 mg/kg [18.2 mg/lb]), which can result in illegal residues when administered for more than the single label dose.

Penicillin G

Penicillin G was one of the first drugs in which the formulation was altered to slow the rate of absorption and thereby extend dosing intervals. The original formulations, potassium and sodium penicillin G, are rapidly absorbed after administration and rapidly eliminated, resulting in 6- to 8-hour dosing intervals to maintain therapeutic plasma concentrations (**Figure 3**). Procaine penicillin G is typically administered once to twice daily because of the slow absorption of penicillin from the injection site and the resulting flip-flop phenomenon. The rate-limiting step is the hydrolysis of penicillin from the procaine moiety that results in a lower maximal plasma concentration, compared with potassium penicillin, but prolonged plasma concentrations. Injection volumes should be ≤ 30 mL/site, but illegal residues can also occur because of inconsistent absorption if the drug is injected into fascial planes.

Administration of benzathine penicillin G results in even lower plasma concentrations because of the slow rate of hydrolysis from the benzathine moiety. Benzathine penicillin G is marketed as a 1:1 mixture with PPG. Benzathine preparations of penicillin result in residues that persist in treated animals longer than those treated with PPG without maintaining therapeutic concentrations against many bacterial organisms.

Oxytetracycline

Oxytetracycline is available as conventional and long-acting formulations. The long-acting formulation induces a prolonged absorption phase resulting in a flip-flop phenomenon and longer dosing intervals than for the conventional formulation (Figure 1). Proprietary differences in the vehicles of the various marketed formulations (polyethylene glycol, propylene glycol, povidone, or pyrrolidone) exist, but all are nonionic surfactants that result in slower drug absorption from the injection site.[9] Rates of absorption after non-IV parenteral administration differ among the formulations, and the individual labels should be consulted for the appropriate WDT. Dosages higher than the labeled dose (20 mg/kg, as a single dose) should not be administered because persistent residues and renal failure can occur.[10,11] Similar to PPG, the injection volume must be limited to provide consistent absorption with typical volumes of ≤ 10 mL/injection site in adult cattle and < 1 to 2 mL/site in calves, with specific label recommendations to that effect for each product.

Florfenicol

Florfenicol is an antimicrobial structurally similar to chloramphenicol, but it lacks the ρ-nitro group that is associated with chloramphenicol-induced aplastic anemia. Florfenicol is formulated in a solution with pyrrolidone, propylene glycol, and polyethylene glycol to decrease the rate of absorption and increase dosing intervals similar to that in long-acting oxytetracycline

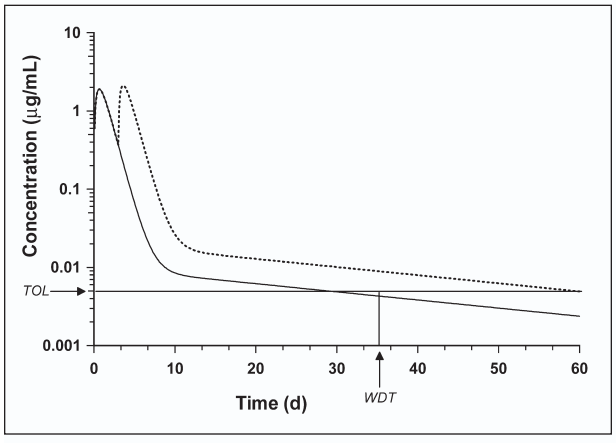

Figure 2—Expected plasma profile of a theoretical drug with a 35-day labeled withdrawal time (WDT) administered as a single dose only (—); notice that the concentration is less than the tolerance (TOL) value before 35 days. However, stacking can occur when a drug with a long terminal half-life is administered for more than 1 dose; notice that if a second dose (····) is administered 3 days after the first dose, the concentration exceeds the tolerance value for 56 days after the second dose, resulting in illegal residues.

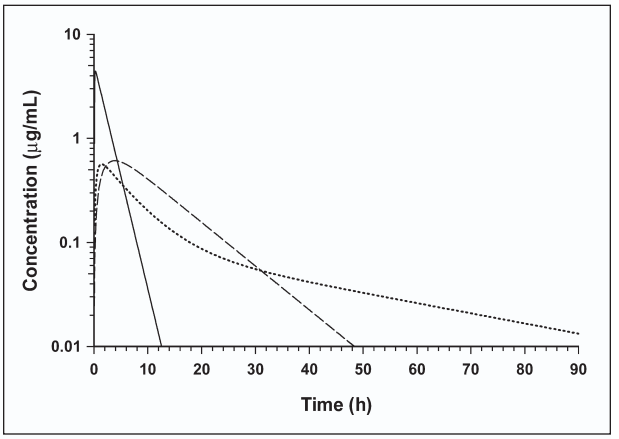

Figure 3—Expected plasma profile for penicillin G after IM administration of 8,000 U/kg (3,636 U/lb) for potassium penicillin G (—), procaine penicillin G (— —), and a 1:1 ratio of procaine and benzathine penicillin G (····) in cattle. Note that the typical minimum inhibitory concentration for pathogenic bacteria is 1 µg/mL.

formulations. A plasma profile similar to that previously described (Figure 1) results after IV and IM administration of the commercially available formulation of florfenicol. The WDT in cattle after 2 doses (20 mg/kg, IM, q 48 h) is 28 days. A single higher dose (40 mg/kg SC) is an alternative treatment option that results in a 38-day WDT. Repeated administration of the higher dose can result in illegal residues (Figure 2). The volume of florfenicol should not exceed 10 mL/injection site regardless of the dosage administered (**New Animal Drug Application [NADA]** 141-063). Florefenicol is excreted in milk[12]; therefore, **Food Animal Residue Avoidance Databank (FARAD)** should be contacted to obtain the most current milk discard recommendations if administered to dairy cattle. Milk can be tested for florfenicol residues by use of chloramphenicol reagents with the Charm II test, which has a 40-ppb sensitivity according to manufacturer's data.[a] Florfenicol is also labeled for use in swine, as an additive to drinking water, with a 16-day WDT (NADA 141-206). The lower WDT in swine is attributable to the lack of a sustained-release mechanism and subsequent lack of the flip-flop phenomenon after oral administration.

Ceftiofur

Ceftiofur is a cephalosporin antimicrobial first licensed for use in the United States in 1988 for treatment of cattle with respiratory tract disease and marketed as a sodium salt (NADA 140-338). Subsequently, in 1996, a hydrochloride salt formulation was approved. That formulation has better in vitro stability because of the change from the sodium salt to the hydrochloride salt, but it results in more tissue irritation after injection. Recently, a new formulation became available, which contained ceftiofur crystalline free acid in a cottonseed oil formulation (NADA 141-209). The cottonseed oil formulation decreases the rate of ceftiofur absorption and causes the flip-flop phenomenon **(Figure 4)** with prolonged maintenance of plasma concentrations.

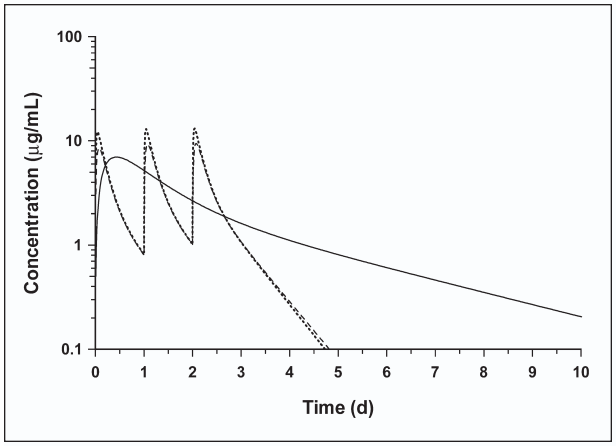

Figure 4—Expected plasma profile for ceftiofur (activity) after SC administration of 2.2 mg/kg (1.0 mg/lb) of sodium ceftiofur (····) and ceftiofur HCl (- - -) once daily for 3 doses (total dose, 6.6 mg/kg [3.0 mg/lb]) and ceftiofur crystalline free acid (——), administered SC as a single injection (6.6 mg/kg). Notice that administration of sodium ceftiofur and ceftiofur HCl results in almost identical plasma profiles.

Administration of sodium ceftiofur results in concentrations in the milk and tissues that do not exceed the tolerance values for cattle, sheep, and goats, which justifies the zero-day meat and milk WDT for the sodium salt formulation. Ceftiofur hydrochloride causes tissue irritation at the IM injection site, which results in injection site residues that exceed the established tolerance value; therefore, a 2-day meat WDT for ceftiofur hydrochloride in ruminants is needed. With its slow absorption, the ceftiofur crystalline free acid formulation does not cause tissue concentrations in beef cattle to reach the tolerance after administration, which justifies a zero-day meat WDT. The injection site, the ear, is discarded at slaughter; therefore, the injection site is not a factor when assessing the withdrawal for on-label use. Extralabel administration of the ceftiofur crystalline free acid formulation by means or locations other than per label can result in prolonged illegal residues and is not recommended. Because other formulations of ceftiofur are approved for use in dairy cattle and other ruminant species, the use of ceftiofur crystalline free acid in those animals is extralabel and not permitted under AMDUCA.[13]

Administration of sodium ceftiofur to swine per label directions results in tissue (kidney) residues that exceed the tolerance; therefore, in contrast to ruminants, a 4-day WDT is necessary. Ceftiofur hydrochloride also has a 4-day slaughter WDT in swine. Ceftiofur crystalline free acid requires a 14-day WDT in swine because of prolonged absorption from the IM injection site (NADA 141-235).

Ivermectin

Ivermectin is an avermectin antiparasitic agent that is effective against gastrointestinal nematodes, lungworms, grubs, and sucking lice and is available in oral, topical, and injectable formulations. Residues and appropriate WDTs after ivermectin administration are dependent on the formulation and route of administration. Ivermectin administered SC (0.2 mg/kg [0.1 mg/lb]) is associated with a slaughter WDT of 35 days in beef cattle because of prolonged residues in the injection site (NADA 128-409). Topical administration of ivermectin as the pour-on formulation (0.5 mg/kg [0.23 mg/lb]) results in a 48-day WDT in beef cattle because of prolonged absorption from the skin (NADA 140-841). The skin acts as a depot for ivermectin; the relative bioavailability (compared with SC injection) is 29.7%, indicating that the amount of the drug absorbed systemically is less and the longer WDT is not caused by a higher dosage, but by slow release from the skin. Ivermectin is also available as a sustained-release bolus, with a 180-day WDT. After administration, the bolus is retained in the rumen or reticulum (similar to magnets used to prevent traumatic reticuloperitonitis), where it releases ivermectin at a constant rate by use of an osmotically driven pump (NADA 140-988).

Conclusions

Formulation and route of administration can have profound effects on the pharmacokinetics and tissue residues of a drug. Proprietary differences in formulations, despite being the same drug, can result in illegal

residues if not used according to label instructions. Intramuscular and SC routes of administration may not be interchangeable; specific recommendations are made for each product. Extralabel use of medications in food animals is only allowable if no approved medication exists or if the approved medication is ineffective. FARAD is available for consultation for instances in which drugs are administered in a different manner than label directions.

a. Charm Sciences Inc, Lawrence, Mass.

References

1. Riviere JE, Webb AI, Craigmill AL. Primer on estimating withdrawal times after extralabel drug use. *J Am Vet Med Assoc* 1998; 213:966–968.

2. Riviere JE. Absorption. In: Riviere JE, ed. *Comparative pharmacokinetics: principles, techniques, and applications*. Ames, Iowa: Iowa State University Press, 1999;21–46.

3. Paige JC, Chaudry MH, Pell FM. Federal surveillance of veterinary drugs and chemical residues (with recent data). *Vet Clin North Am Food Anim Pract* 1999;15:45–61.

4. Korsrud GO, Boison JO, Papich MG, et al. Depletion of intramuscularly and subcutaneously injected procaine penicillin G from tissues and plasma of yearling beef steers. *Can J Vet Res* 1993; 57:223–230.

5. Pyorala S, Laurila T, Lehtonen S, et al. Local tissue damage in cows after intramuscular administration of preparations containing phenylbutazone, flunixin, ketoprofen and metamizole. *Acta Vet Scand* 1999;40:145–150.

6. Welsh EM, McKellar QA, Nolan AM. The pharmacokinetics of flunixin meglumine in the sheep. *J Vet Pharmacol Ther* 1993;16: 181–188.

7. Anderson KL, Neff-Davis CA, Davis LE, et al. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res* 1990;51:1464–1467.

8. Toutain PL, Bousquet-Melou A. Plasma terminal half-life. *J Vet Pharmacol Ther* 2004;27:427–439.

9. Baggot JD, Brown SA. Basis for selection of dosage form. In: Hardee E, Baggot JD, eds. *Development and formulation of veterinary dosage forms*. 2nd ed. New York: Marcel Dekker Inc, 1998;7–144.

10. Vaala WE, Ehnen SJ, Divers TJ. Acute renal failure associated with administration of excessive amounts of tetracycline in a cow. *J Am Vet Med Assoc* 1987;191:1601–1603.

11. Vivrette S, Cowgill LD, Pascoe J, et al. Hemodialysis for treatment of oxytetracycline-induced acute renal failure in a neonatal foal. *J Am Vet Med Assoc* 1993;203:105–107.

12. Soback S, Paape MJ, Filep R, et al. Florfenicol pharmacokinetics in lactating cows after intravenous, intramuscular and intramammary administration. *J Vet Pharmacol Ther* 1995;18:413–417.

13. Webb AI, Baynes RE, Craigmill AL, et al. Drugs approved for small ruminants. *J Am Vet Med Assoc* 2004;224:520–523.