

Extralabel intramammary use of drugs in dairy cattle

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Extralabel intramammary administration of drugs occurs with some regularity in dairy cattle, most commonly in association with mammary gland infections (mastitis) that fail to respond to approved products. To comply with AMDUCA regulations, extralabel drug use must include a sufficiently extended withdrawal interval so that no residues are found in meat or milk products. This is particularly important when using products via intramammary administration because milk residue violations can have serious economic consequences for the producer and veterinarian. For some of the drugs listed in this report, well-conducted pharmacokinetic studies have been performed to define appropriate withdrawal intervals after intramammary administration in cattle, whereas for others, the recommendations may have been formulated on the basis of limited data. To ensure food safety and avoid residue violations, it is extremely important for veterinarians to maintain good records and follow extended withdrawal intervals when using intramammary administration of drugs in an extralabel manner. Producers should also be requested to test milk samples from treated cows with an appropriate rapid residue screening assay when a drug residue might be present.

Ceftiofur

Ceftiofur sodium^a and ceftiofur hydrochloride^b are approved for IM and SC use only, and label use does not result in drug concentrations in milk greater than the tolerance limit set by the FDA of 0.1 µg/mL (100 ppb). Therefore, ceftiofur has a zero milk withholding time. Occasionally, these antimicrobials have been used in an extralabel manner by bovine practitioners or dairy producers for the intramammary treatment of coliform mastitis. This practice does result in milk concentrations greater than the toler-

ance limit, and residues can persist for up to 168 hours (7 days) after the last dose.¹ Furthermore, a new ceftiofur product^c has recently been approved for intramammary use in lactating dairy cattle and has a 72-hour milk withdrawal time. Under the guidelines of AMDUCA, the intramammary use of ceftiofur sodium^a or ceftiofur hydrochloride^b would be illegal now that an approved formulation exists.

Chlorhexidine

Chlorhexidine solution^d is occasionally used to cause cessation of lactation in chronically infected mammary gland quarters. After intramammary infusion of chlorhexidine (two 28-mL doses given 24 hours apart), no residues were detected in milk from untreated mammary gland quarters; however, chlorhexidine was detected in milk from treated quarters throughout the duration of the 42-day study.² When intramammary administration of chlorhexidine is used to stop lactation in a mammary quarter, the objective is to not milk that quarter for at least the remainder of the lactation. However, accidental milking of a treated mammary gland quarter may cause a chlorhexidine residue in the bulk milk tank for an extended period. Although no legal limit has been established for milk, the FDA has set a tolerance limit of zero for chlorhexidine residues in edible tissues of calves.³ The authors of that study concluded that on the basis of the long elimination half-life of chlorhexidine in milk and the FDA's published zero tolerance for chlorhexidine residues, intramammary administration of chlorhexidine was not recommended. The use of povidone-iodine for therapeutic cessation of lactating mammary gland quarters is preferred to use of chlorhexidine.

Florfenicol

Florfenicol is not approved for use in dairy cattle > 20 months of age; however, the Food Animal Residue Avoidance Databank (FARAD) occasionally receives calls from practitioners requesting milk withdrawal information after intramammary administration of the drug. Systemic absorption of florfenicol after intramammary administration does occur in dairy cattle, and in 1 study,⁴ serum concentrations were greater than those detected after IM administration. In that study,

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the terminal elimination half-life of florfenicol in milk after intramammary administration of 20 mg/kg was 235 minutes, and florfenicol residues were not detected after 48 hours. The Charm II assay^c (which is often used by milk processing plants) can detect chloramphenicol at a concentration of 1 ppb and florfenicol at concentrations of 35 to 40 ppb. Any detectable concentration of florfenicol in milk would be considered violative. By use of the half-life and highest concentration in milk observed in the study by Soback et al,⁴ FARAD calculates that it would take 80 hours to deplete from 1,000 ppm to 1 ppb. Because variability in excretion of florfenicol in milk may be large, FARAD recommends an initial withdrawal interval of 120 hours for milk from treated cows (Table 1), followed by testing to ensure that residues are indeed undetectable.

Gentamicin

Several veterinary organizations, including the AVMA, American Association of Bovine Practitioners, and Society for Theriogenology, have established or support policies that discourage the extralabel use of aminoglycosides in food animal species. However, these voluntary-ban position statements are nonbinding, and extralabel use of gentamicin in cattle continues to occur. Although not approved, gentamicin is most commonly given by the intramammary route for the treatment of dairy cattle with coliform mastitis, and this practice continues to cause both milk and meat residue violations.^{5,6} The safe concentration for gentamicin concentrations in milk is considered to be 0.03 µg/mL (30 ppb).

Following a single intramammary infusion of 500 mg of gentamicin, drug concentrations in milk remained greater than the 0.03 µg/mL concentration for 84 hours.⁷ However, after multiple intramammary administrations of gentamicin (500 mg, q 12 h, for 5 days), detectable milk concentrations persisted for 132 hours (6 days) after the last administration. Milk residues persisted even longer when intramammary administration was combined with IM use of the drug, and gentamicin concentrations remained > 0.03 µg/mL for 228 hours (10 days). FARAD strongly discourages intramammary administration of gentamicin in dairy cattle; however, if it is used, FARAD recommends a milk withdrawal period of at least 10 days after the last treatment. Veterinarians are cautioned that the intramammary use of gentamicin is likely to be associated with prolonged tissue residues in cattle.

Oxytetracycline

Although commonly recommended as an extralabel antimicrobial treatment for dairy cattle with masti-

tis,⁸ oxytetracycline is rarely given by the intramammary route. The drug penetrates the mammary gland very well and achieves high concentrations in milk when given by either IV or other parenteral routes.⁹ A commercial formulation of long-acting oxytetracycline^f is approved for lactating dairy cattle that permits marketing of milk 96 hours after IM or SC administration. The FDA has established a tolerance of 0.3 µg/mL (300 ppb) in milk on the basis of the sum of all tetracycline residues detected in a sample. A new long-acting product containing oxytetracycline at 300 mg/mL^g has been approved for use in beef cattle and nonlactating dairy cattle. That drug has a significantly longer milk withdrawal time after IM administration, with residues persisting in milk samples for 25 days.¹⁰ Extralabel use of that product in lactating dairy cattle is not recommended. After intramammary administration into a single mammary gland quarter, oxytetracycline is systemically absorbed and can cause residues in milk from all quarters for up to 132 hours.¹¹ Although no formulations of oxytetracycline are presently approved for intramammary use in cattle, all milk from a cow given an extralabel treatment should be discarded for a minimum of 6 days after the last treatment. An extended slaughter withdrawal interval of 28 days is also recommended because of systemic absorption of the drug from the mammary gland.

Polymyxin B

Polymyxin B is a narrow-spectrum antimicrobial with good in vitro activity against gram-negative bacteria, including coliforms (ie, *Escherichia* and *Klebsiella* spp) and *Pseudomonas* spp. The high cost of the drug and its substantial nephrotoxicity generally prohibit systemic administration, although topical administration of the drug is practiced. Although it is not approved for use in ruminants, intramammary infusions of 1 to 2 million units (100 to 200 mg) of polymyxin B/quarter have been used to treat cows with severe cases of mastitis caused by gram-negative organisms. After intramammary infusion, the drug was not systemically absorbed from normal udders, although substantial blood and urine polymyxin concentrations were detected after infusion in an acutely inflamed udder.¹² The drug was also detected in milk from nontreated quarters. After administration of 2 million units of polymyxin B (prepared in 10 mL of distilled water) into a single quarter (3 doses given 12 hours apart), residues were detected for up to 108 hours (4.5 days) after the last treatment (limit of detection, 0.5 U/mL [0.05 µg/mL] of milk).¹² There is no tolerance limit established for polymyxin in milk either in the United States or in other countries. FARAD recommends that all milk from a cow given polymyxin B should be discarded for a minimum of 7 days after the last intramammary administration.

Povidone-iodine

This drug is also given by the intramammary route for cessation of lactation in chronically infected mammary gland quarters.¹³ Although studies examining the elimination kinetics of povidone-iodine after intra-

Table 1—Food Animal Residue Avoidance Databank recommended withdrawal interval (WDI) after extralabel intramammary administration of various drugs in dairy cattle.

Drug	Dose	Meat WDI (d)	Milk WDI (d)
Florfenicol	20 mg/kg	28	5
Gentamicin	500 mg/quarter	180	10
Oxytetracycline	500 mg/quarter	28	6
Polymyxin B	1–2 × 10 ⁶ U/quarter	2	7

mammary infusion in cows have not been published, povidone-iodine may be less likely to cause milk residues than chlorhexidine. Povidone-iodine is more effective than chlorhexidine in causing complete cessation of lactation after intramammary administration.¹³ Seventy-one percent of the mammary gland quarters treated with chlorhexidine continued to function (produce milk) at some level, whereas all povidone-iodine-treated quarters ceased milk production completely. Because povidone-iodine is very effective in completely eliminating all secretion from a treated mammary gland quarter, it is likely a better choice for therapeutic cessation of lactation because the residue risk should be minimal if no secretion (milk) is produced. However, it should be emphasized that this represents extralabel use of a drug, and because appropriate milk withdrawal data are not available, extra care must be taken to avoid milking treated mammary gland quarters, which could potentially lead to residues.

Other Drugs

Tilmicosin and spectinomycin are 2 other antimicrobials for which FARAD occasionally receives calls requesting milk withdrawal times after intramammary use in cattle. Unfortunately, pharmacokinetic data regarding intramammary administration of these drugs have not been published, and appropriate withdrawal recommendations cannot be made at this time. FARAD occasionally receives requests for milk withdrawal times regarding intramammary administration of enrofloxacin, sulfonamides, and dimethyl sulfoxide. It is important to emphasize that any extralabel use of these drugs is prohibited in food animals and cannot be justified under any circumstances.¹⁴

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- a. Naxcel, Pharmacia Animal Health, Kalamazoo, Mich.
 - b. Excenel, Pharmacia Animal Health, Kalamazoo, Mich.
 - c. Spectramaster LC, Pharmacia Animal Health, Kalamazoo, Mich.
 - d. Nolvasan suspension, Fort Dodge Animal Health, Fort Dodge, Iowa.
 - e. Charm II System, Charm Sciences Inc, Lawrence, Mass.
 - f. Liqumycin LA-200, Pfizer Animal Health, New York, NY.
 - g. Tetradure, Merial, Duluth, Ga.
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