

Prevention of antibiotic residues in veal calves fed colostrum

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Intramammary administration of antibiotic preparations at cessation of milking is a basic component of most mastitis control programs. Similarly, timely and adequate colostrum administration to neonatal calves is essential for calf health and survival. Companies developing new treatments for nonlactating cows are required to submit tissue and milk residue depletion data for determination of slaughter and milk withholding times for treated cows. However, the issue of antibiotic tissue residues in calves consuming colostrum is not addressed. "Special-fed" ("milk-fed") veal calves are typically slaughtered at 16 weeks of age, providing some assurance that residues from colostrum ingestion will not be an issue. In contrast, bob veal calves are killed within the first 3 weeks of life. Tissue residues resulting from colostrum ingestion have been detected in calves slaughtered several days after birth.¹

Veterinary pharmaceutical companies are not required to perform studies examining drug residues in calves fed colostrum. Without appropriate studies, estimation of preslaughter withholding times for such calves is extremely difficult. To make this estimation, numerous factors have to be considered, including drug type and concentration, duration that cows are not lactating, drug persistence in mammary secretions, volume of colostrum ingested and rates of fractional absorption, metabolism, and excretion of the drug. In addition, the influence of a sustained release formulation (eg, penicillin benzathine G vs penicillin sodium G) or slow-release vehicle (eg, mineral or peanut oil) must be considered.

The purpose of this article is to provide practitioners with meat withdrawal interval (WDI) recommendations for veal calves fed colostrum from cows treated at the cessation of lactation. These recommendations assume that the period between treatment of the cow and calving specified on the product label has been observed. Conservative estimations or assumptions

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References for determinations are available on written request.

Table 1—Estimated slaughter withdrawal intervals (WDI) for veal calves exposed to colostrum of cows treated during the nonlactation period

Product	Label minimum nonlactation period (d)	Label preslaughter withdrawal time for cull cows (d)	Label milk discard time (h)	FARAD estimated WDI for calves (d)
Cephapirin benzathine (300 mg/syringe)				
Cefa-Dri (Fort Dodge)	30	42	72	7
Tomorrow (Franklin)				
PPG (100,000 IU/syringe)				
Go-Dry (GC Hanford)	Assuming period of 26 days*	14	72	4
First Choice (Ken Ag)				
Dihydrostreptomycin (1 g/syringe + 1 million IU PPG)	42	60 (nor within 4 days of calving)	96	30
Quartemaster (Pharmacia-Upjohn)				
Novobiocin				
Biodry (400 mg/syringe) (Pharmacia-Upjohn)	30	30	NL	4
Albadry Plus (with 200,000 IU PPG) (Pharmacia-Upjohn)	30	30	72	4
Cloxacillin benzathine (500 mg/syringe)				
Dry-Clox (Fort Dodge)	30	30	NL	20
Orbenin-DC (Pfizer)	28	28	NL	20
Erythromycin (600 mg/syringe)				
Erythro-Dry (Merial)	Assuming period of 30 days*	14 (nor within 4 days of calving)	NL	10†
Gallimycin-Dry (Merial)				
Gallimycin-Dry Cow (Agnilabs)				

*Product label does not mandate a minimal nonlactation period. †Label veal withdrawal time rather than FARAD estimated withdrawal interval.
PPG = procaine penicillin G; NL = none listed.

have been used to minimize the risk of residues. A summary of the FARAD WDI recommendations for all preparations marketed in the United States for nonlactating cows is provided (Table 1). Also included are label minimum periods, label preslaughter times for cull cows, and label milk discard times following calving.²

Cephapirin Benzathine

Cephapirin benzathine (CB) is a first generation cephalosporin, primarily having a gram-positive spectrum. This compound has an established US tolerance level of 0.02 ppm in milk and 0.1 ppm in uncooked tis-

sue of cattle. Both CB-containing products marketed in the United States contain 300 mg of CB/syringe. If label requirements of a 30-day interval between treatment and calving are observed, milk from most cows will contain CB residues of < 0.02 ppm at parturition. Using the highest reported colostrum or milk residue measurements following label treatment (0.32 ppm) and assuming calf fluid consumption of 1 gal/d for 3 days (label milk-discard time), calf exposure is calculated at 3.65 mg. Assuming 100% per os absorption and complete accumulation in the kidney, this would result in approximately 27 ppm in the kidney. Tissue depletion data are not available. Using the longest reported plasma half-life of 13.3 hours,³ it would require approximately 7 days for kidney residues to decline to less than the tolerance level.

Procaine Penicillin G

Historically, administration of penicillin to nonlactating cows has been instrumental in reducing the frequency of infections caused by *Streptococcus agalactiae* and *Staphylococcus aureus*, the 2 major contagious mastitis pathogens. The US tolerance level for penicillin in edible tissues of cattle is 0.05 ppm. Although not an official tolerance level, a safe level for penicillin in milk has been established at 0.005 ppm by the FDA. All of the penicillin-containing products marketed in the United States for intramammary administration to nonlactating cows use the water-insoluble procaine salt of benzylpenicillin (procaine penicillin G [PPG]). Two of these products contain PPG as the sole active ingredient and have 100,000 IU of penicillin activity in an oil vehicle/syringe. Calculation of WDI for veal calves is particularly problematic for these 2 products because labels do not mandate a duration of the nonlactation period. Limited data would suggest that a nonlactation period of 3 weeks allows penicillin residues in the cow's secretions to decrease to approximately 0.01 ppm.⁴ Calf-feeding studies using milk fortified with PPG suggest that these concentrations are not likely to result in veal residues.⁵ In a study performed by the Bureau of Veterinary Medicine (now the Center for Veterinary Medicine) using an intramammary infusion of 1 million U of PPG/mammary quarter and a nonlactation period of at least 26 days in which cows were not lactating, penicillin residues were not detected in tissues of calves fed colostrum for 4 days and then slaughtered 4 days later.⁶ On the basis of this evidence, a meat WDI of 4 days is recommended for calves exposed to colostrum of cows having had a nonlactation period of at least 26 days. In the event that the nonlactation period is unknown or absent, Canadian studies⁶ in which high doses of PPG were administered IM suggested that violative residues in veal calves could be prevented with a 10-day WDI.

Dihydrostreptomycin Sulfate

One syringe marketed in the United States contains 1 million IU of PPG and 1 g of the aminoglycoside dihydrostreptomycin sulfate (DHS). The US tolerance levels for DHS are 0.125 ppm in milk, 2.0 ppm in the kidney, and 0.5 ppm in other uncooked tissues of cattle. Data describing depletion of DHS in the mammary

gland after treatment are scarce. Two studies^{4,7} suggest that after an initial rapid depletion of DHS, a low concentration of the drug persists for an extended period (at least 5 weeks). Mean concentrations of DHS in secretions from nonlactating cows decrease to approximately 11 ppm by 5 weeks after treatment.⁴ At this concentration, a small calf consuming 1 gal of colostrum or milk/d during the approved 4-day milk-discard period could be exposed to 6 mg of DHS/kg (2.7 mg/lb) of body weight. Oral absorption data for DHS are not available, but per os bioavailability of most compounds typically is high in neonatal calves. Tissue data suggest that kidney residues decrease below the tolerance level within 30 days after IM administration of between 7 and 10 mg of DHS/kg (3.2 and 4.5 mg of DHS/lb).⁸ Only one study⁸ has examined DHS tissue residues in veal calves fed colostrum following treatment of their dam. In that study, residues in calf urine (but not tissue) persisted for up to 1 month after feeding colostrum from treated cows that had not lactated for periods ranging from 4 to 75 days. A WDI of 30 days represents a conservative extended withdrawal period consistent with the limited data available.

Novobiocin

A derivative of coumarin, novobiocin (NB) is primarily used to treat staphylococcal and streptococcal infections in dogs, poultry, mink, and mastitic cows. The compound is excreted in bile and undergoes enterohepatic circulation. The US tolerance levels for NB are 1 ppm for edible tissues and 0.1 ppm in milk. Both of the preparations marketed in the United States for use in nonlactating cows use the more water-soluble sodium salt in an oil suspension, rather than the less soluble calcium salt. Studies⁹ indicate that, in most cows treated with 400 mg of NB, udder secretion concentrations decrease to < 0.1 ppm by 30 days. A calf consuming 1 gal of milk/d containing 0.1 ppm of NB during the 3-day milk-discard period will have a total oral exposure of 1.14 mg. Assuming complete accumulation in the liver, residues should not exceed a tissue tolerance level of 1 ppm. An extended extralabel WDI of 4 days for calves consuming colostrum is recommended. For compounds containing an additional 200,000 IU of PPG, a WDI of 4 days should also be sufficient.

Cloxacillin Benzathine

The primary veterinary application of cloxacillin benzathine (CXB), a semisynthetic penicillin resistant to penicillinase, is for treatment and prevention of bovine staphylococcal mastitis. The US tolerance level for CXB is 0.01 ppm for milk and tissue. Both CXB-containing products marketed in the United States for treatment of nonlactating cows contain 500 mg of the water-insoluble benzathine salt in an oil vehicle. Like DHS, CXB appears to be particularly persistent in udder secretions of nonlactating cows. Results of 2 studies have shown residues between 3 and 4 ppm following a 30-day period in which cows were not lactating.¹⁰ A calf consuming 1 gal of colostrum containing 4 ppm of CXB/d during a conservative 4-day milk-discard period will have an oral exposure of 60.8 mg. Bioavailability and tissue residue depletion data in ruminants do not

exist. Elimination half-lives from various tissues (including kidney) in hens, rabbits, and rats range from 0.2 to 21 hours.¹¹ Assuming complete accumulation in the kidney and a half-life of 24 hours, residues should deplete to less than the tolerance level by 16 half-lives. The FARAD recommendation of a 20-day WDI for colostrum-exposed veal calves represents a conservative estimate based on the extremely limited data available.

Erythromycin

Main mastitis applications of erythromycin (ERY), a macrolide having primarily a gram-positive spectrum, have focused on treatment of penicillin-resistant staphylococcal infections. Elimination is principally through hepatic metabolism and biliary excretion, and the liver contains the highest organ residue concentration. The US tolerance level for ERY in edible tissue of cattle is 0.1 ppm. Although not an official tolerance level, a "safe level" for milk has been established at 0.05 ppm by the FDA. Preparations in the United States for nonlactating cattle contain 600 mg of the free-base form of ERY in an oil vehicle. As with PPG preparations, product labels for ERY do not mandate a minimum nonlactation period. However, using the longest reported half-life of approximately 1 day in udder secretions from nonlactating cows,¹² total drug concentration in colostrum would be negligible by the end of a modest 30-day period (0.002 µg/ml). Of the preparations marketed in the United States, only those containing ERY have a veal calf label withholding time (10 days). Transplacental transfer of ERY is known to occur in humans, and the label withholding time of 10 days for veal should prevent development of any residues.

General Recommendations

After infusion into the udder, compounds contained in treatments for nonlactating cows are slowly absorbed into the blood, metabolized, and then excreted. The FARAD recommendations assume the product label's minimum nonlactation period has been observed. Premature calving or management errors may result in a premature return to milking. In either case, higher than expected drug concentrations may be in the colostrum. In cases in which the product label's minimum period has not been observed, practitioners are encouraged to contact FARAD for more specific recommendations.

At least 1 unpublished study (involving use of a PPG-DHS-containing dry treatment) found that still-born calves may contain tissue residues.* Presumably, this results from transplacental transfer of antibiotic from the cow. For this reason, veterinarians should warn clients that a calf that has not suckled or been treated may still contain residues from its dam. Additionally, veterinarians should inform farmers that pooled or saved colostrum may produce residues in calves if it comes from a dam treated with antibiotics.

Producers who do not raise all calves born on their dairy are placed in the difficult position of selling animals that potentially contain violative

residues. Veterinarians recommending or prescribing treatment of nonlactating cows without addressing the impact of veal residues may be incurring regulatory liability. Consulting veterinarians can assist dairy producers in constructing record-keeping procedures that will minimize regulatory exposure if residues are detected. For veal calves, producers should provide written documentation to the buyer that warns of this possibility and that designates a date after which calves can be slaughtered for food. The farmer should retain a copy of this documentation, which is signed by the buyer or the buyer's agent at the time calves are transported off of the premises. In the event that calves are prematurely slaughtered, this documentation helps absolve the producer of any responsibility. At least 1 state, California, provides a form specifically for the purpose of informing animal buyers of pending WDI. This form is not specific to calves and can be applied to an animal of any age or species.

The WDI found in this article were based on limited data available from the literature and veterinary pharmaceutical companies. New research addressing the question of colostrum-transferred drug residues is currently underway. The FARAD will continue to collect and summarize this information.

*FDA Bureau of Veterinary Medicine. DVMR research projects 158 and 159: study on residual penicillin-dihydrostreptomycin in tissues of veal calves. Rockville, Md: Unpublished data, 1979.

References

1. Antibiotic residues transmitted by bovine colostrum. *J Am Vet Med Assoc* 1979;175:819.
2. Arrijoja-Dechert A, ed. *Compendium of veterinary products*. 4th ed. Port Huron, Mich: North American Compendiums Inc, 1997-1998.
3. Nouws JFM, Ziv G. A kinetic study of beta-lactam antibiotic residues in normal dairy cows. *Zentralbl Veterinarmed [A]* 1978;25:312-326.
4. Pugh KE, Harris AM, Marshall MJ, et al. Evaluation of a long-acting intramammary preparation containing high doses of penicillin and streptomycin for use in dry cows. *Vet Rec* 1973;93:212-216.
5. Prange RW, Oliver SP, Duby RT, et al. Residues in young veal calves after consumption of milk containing penicillin. *J Dairy Sci* 1984;67:2970-2973.
6. 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.
7. Ziv G, Saran-Rosenzuaig A, Gluckman E. Kinetic considerations of antibiotic persistence in the udders of dry cows. *Zentralbl Veterinarmed [B]* 1973;20:425-434.
8. Heitzman RJ. *Dihydrostreptomycin streptomycin. Residues of some veterinary drugs in animals and foods*. FAO food and nutrition paper No. 41/7. Geneva: FAO/WHO, 1995.
9. Schultze WD, Mercer HD. Nonlactating-cow therapy with a formulation of penicillin and novobiocin: mammary irritation and residues. *Am J Vet Res* 1976;37:1281-1284.
10. Ziv G, Saran-Rosenzuaig A, Riesenberger R. Retention of antibiotics in dry-udder secretions after the infusion of several "dry cow" antibiotic products. *Zentralbl Veterinarmed [B]* 1973;20:415-424.
11. Acred P, Brown DM. Further pharmacology and chemotherapy of cloxacillin. *Br J Pharmacol* 1963;21:339-354.
12. Ziv G. Practical pharmacokinetic aspects of mastitis therapy-3: intramammary treatment. *VM SAC* 1980;75:657-670.