Antibiotic Treatment of Lactating Cows

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The food animal practitioner of today faces a number of dilemmas when deciding how to treat a sick lactating cow with an antibiotic. What is the most effective drug? What dose? Is the drug approved for use in lactating cows? If so, is it approved at the dose he or she wants to prescribe? Is it approved by the route of administration he or she wants to use? If the drug is used in an extralabel manner, what should be the recommended withdrawal time for milk? Can the withdrawal time be accurately confirmed by a cowside residue test?

Several drugs will not be discussed in detail in this paper. There has been a voluntary moratorium against the use of gentamicin and other aminoglycosides in cattle since October 1994. All sulfonamides except sulfadimethoxine have been prohibited in lactating dairy cows since July 1992. Dihydrostreptomycin is no longer available in combination with penicillin, and so essentially is not being used. Tilmicosin results in excessive periods of milk residues, up to 31 days in one study, and so should be avoided.[1]

Table 1 lists the antimicrobials approved for use in lactating cows.[2] A recent survey asked veterinary practitioners what drugs they actually were using in lactating dairy cows, and with what frequency.[3] Fifteen of the 25 most-used drugs were antimicrobials, and of these all but 3 were approved for use in lactating dairy cattle. (Table 2) Of these 3 only oxytetracycline was frequently used. Four of the five most-used antimicrobials were approved beta-lactams for which sensitive residue tests are available. The study showed that veterinary practitioners prefer to use approved products. However it did not provide information as to whether practitioners were using approved dosages and routes of administration for these products.

Table 1. Antimicrobials approved for use in lactating cows.

Injectable	Intramammary	Oral	Feed Additive
Amoxicillin	Amoxicillin	Neomycin	Chlortetracycline
Ampicillin	Cephapirin	Sulfadimethoxine	Oxytetracycline
Ceftiofur	Cloxacillin		Topical
Erythromycin	Erythromycin		Furazolidone
Procaine Penicillin G	Hetacillin		Neomycin
Sulfadimethoxine	Novobiocin		Nitrofurazone
	Procaine Penicillin G		Oxytetracycline
	Pirlimycin		Polymyxin B

Table 2. Antimicrobials used in lactating cows by practitioners (1993 survey)

Antimicrobial	Frequency of Use
Procaine Penicillin G	5 times/week
Ceftiofur Oxytetracycline*	1 to 5 times/week
Cloxacillin Cephapirin Ampicillin Sulfadimethoxine	1 to 4 times/month
Nitrofurazone (topical) Erythromycin Amoxicillin Tetracycline Hetacillin Spectinomycin* Gentamicin*	1 to 12 times/year
Dihydrostreptomycin	<1 time/year

*Not approved for use in lactating cows
Abstracted from Sundlof *et al.*, 1995

Effect of increased dosage

Use of unapproved dosages of antimicrobials may change the required withholding time for milk and meat. One example of this is procaine penicillin G, which is approved at 6600 I.U./kg (3000 I.U./lb) once daily. At that rate, the withdrawal time for meat is 10 days. In feedlot steers, an IM dose of 66,000 I.U./kg SID was preferred to 24,000 I.U./kg SID for providing a Mini-

mum Inhibitory Concentration in serum or plasma of 0.5-2.0 μg/ml.[4] At that rate, the withdrawal time for meat became 21 days. In Holstein calves treated IM with oxytetracycline daily for 3 days, residues could be detected 19 days postinjection at the injection sites for all doses used (6.7 mg/kg, 13.4 mg/kg, or 20.0 mg/kg).[5] Significant residues were detected at 19 days postinjection in the kidneys of calves receiving the two highest doses and also in the noninjected muscle tissue of the calves receiving the highest dose. The lowest dose was the label approved dose, for which the recommended withholding time for meat is 18 days.

Approved doses of some drugs include a recommendation for a maximum volume to be injected at each site. This volume is frequently 10 ml. Increasing the volumes of injection at intramuscular sites generally results in a decreased absorption rate and a lower maximum concentration of the drug in the blood.[4] The prolonged absorption could result in a need for prolonged milk withholding for an unknown and variable period of time. The significance of this effect varies with the drug, carrier, and actual volume used.

Use of different routes of administration

There can be several consequences of using antimicrobials by unapproved routes of administration. Decreased rates of absorption or failure of the drug to distribute to certain tissues may render the drug ineffective because therapeutic concentrations do not reach the site of infection. Specific examples are pirlimycin and cephapirin, approved for intramammary use, which have failed to provide minimum inhibitory concentrations against *Staphylococcus aureus* in the mammary gland when adminstered intramuscularly.[6,7] Another consequence of using an unapproved route of administration is the withholding time may change. Ceftiofur is approved for intramuscular administration only. When used in this manner, therapeutic concentrations do not occur in milk.[8,9] Intramammary use results in therapeutic concentrations in milk, but then zero-withholding of milk no longer applies.

The effect of using different routes of administration, even using different muscle groups for IM injection has been demonstrated in feedlot calves.[4] Procaine penicillin G was administered at 66,000 I.U./kg in the gluteal muscles, neck muscles, or subcutaneously over the neck. The half-life of the drug was 15.96, 8.85, and 18.08 hours for IM gluteal, IM neck, and SC neck, respectively. Maximum concentration of penicillin in the plasma(C_{MAX}) was 2.63, 4.24, and 1.85 μg/ml for the same respective groups. The numbers were not significantly different, possibly because of small numbers of animals used. The increased bioavailability of drug from neck muscles compared to the other IM site and the prolonged half-life and decreased C_{MAX} following SC administration suggest that these factors might influence milk withholding times in lactating cows.

The intrauterine (IU) route of administration is a less efficient route than intramuscular.[10] In addition, absorption is variable resulting in the need for rather prolonged withholding times in relation to the amount of drug administered.[11-14] Using a high-performance liquid chromatography test, oxytetracycline was quantitated in milk after IV (16.5 mg/kg), IM (11.0 mg/kg) or IU (2 g) administration to lactating dairy cows. The times for oxytetracycline in milk to decline to <30 ppb in each group of 6 cows ranged from 72 to 84 hours after IV treatment, 84 to 96 hours after IM treatment, and 24 to 144 hours after IU treatment.[14] This information might be compared to current recommendations from the Food Animal Residue Avoidance Databank which are to withhold milk for 96 hours after a single dose of 3 g IU, then test the milk before keeping it, or 120 hours after a single dose of 4 to 6 g IU, then test.[15] One might pose the question of what should milk withholding be for treatment protocols for retained fetal membranes where IU oxytetracycline is recommended daily or every other day until the animal's condition has improved?[16]

Residue tests to confirm withholding times for milk

After extralabel use of an antimicrobial drug in a lactating dairy cow, a reasonable withholding is recommended based on our knowledge of the pharmacokinetics of the antimicrobial drug in question. A negative residue test is then often recommended as a precaution before milk from the treated cow is added to the bulk tank. Results of residue tests have generally been accepted to represent reality, with positive results interpreted to mean a prolonged presence of the antimicrobial in the milk of the cow. Residue tests have been used to suggest that routine withholding times suggested by veterinarians were inadequate.[17] However, results from some of the commonly used microbial inhibition tests should be viewed with suspicion, particularly when used as cowside tests on individual animals.[18] A variety of commercially available residue tests were used on milk from 172 cows with mild to moderate mastitis. One hundred of the cows received intramammary treatments with amoxicillin or cephapirin. The remaining cows were treated with oxytocin prior to 3 milkings. Milk samples were collected pretreatment, at milking #4, milking #9 or 11, and day 21 posttreatment. Samples from all pretreatment and day 21 samples, and all oxytocin treated cows were presumed to be negative for antimicrobials. Looking at just these presumed negative samples, the following false positive rates were found: CITE probe beta lactam 43.6%; Delvotest-P 37.7%; Charm Farm 81.7%; LacTek beta lactam 2.6%; *Bacillus stearothermophilus* disk as-

say 18.8%. Significant false positive rates have also been reported in cows with endotoxin-induced mastitis that had not received any antimicrobials.[19] A wide variation in positive rates were obtained from different tests used before treatment and after the recommended withholding in cows that had received intramammary amoxicillin.[20] False positives ranged from 0 to 60% in pretreatment samples. Knowing this information, the range of 0 to 67% positives after the withholding period makes it difficult to interpret reality about persistence of drug in the milk. At least part of the problem is that milk samples have biological diversity, varying in their degree of bacteriologic contamination, somatic cell counts, and natural antimicrobial substance activity.[21] Thus, antimicrobials are not the only substances that may be found in milk that can inhibit bacterial growth and trigger positive test results. Another point is that the residue tests are often validated on spiked samples of pooled milk from normal cows, while the tests are run on milk from recuperating sick cows. The tests may also simply determine the presence or absence of an antimicrobial without distinguishing whether the amount present is above or below the recognized tolerance level.[22]

The potential influence of inaccurate microbial inhibition assays in previously reported research must be considered. Erskine *et al.* described erratic results in their study of ceftiofur in normal and mastitic cows where milk concentrations of ceftiofur did not follow serum concentrations, particularly in mastitic cows.[8] They considered "either that ceftiofur activity persists.....or that bioassays with high sensitivity identify antimicrobial activity from endogenous sources". We can only speculate on the impact of the accuracy of residue tests on numerous other research reports in recent years.

The future holds hope for more accurate information as more sensitive quantitative tests are developed that do not rely on microbial inhibition. High-pressure liquid chromatography (HPLC) with a sensitivity of 2 ng/ml (ppb) was used to classify 292 milk samples from cows treated with oxytetracycline relative to the FDA safe concentration (≤30 ng/ml).[22] The results were compared with determinations made with the Charm II test, a radioimmunoassay. A total of 48 of the 292 test results (16.4%) did not agree, with all but one being the Charm II test identifying as violative 47 samples that had <30 ng oxytetracycline/ml. The Charm II test was discussed as being an appropriate screening test, because violative samples did not slip through. However, the tendancy for it to yield presumptive-violative test results at concentrations lower than the FDA safe concentration suggested that it should not be the sole basis on which to decide to reject milk. The reality of the problem has become evident with an increasing number of insurance claims in 1995 for "antibiotics in milk" by producers who suddenly are unable to identify the source of the adulteration.[23] In fiscal year 1994, the National Drug Residue Milk Monitoring Program reported that of 33 tankers of milk determined to have violative residues of antibiotics by screening tests, only 8 were verified for a 75% false positive rate.[24] In the first quarter of 1995, when the practice of using the same screening test as its own confirmatory test went into use, only 3 of 48 presumptive violative samples could be confirmed for a 94% false positive rate. Although the percentage of tankers of milk that trigger positive results may be small, the number of false positive tests is significant when considering that each one results in a dairy producer being penalized.[23]

Alternatives to antibiotics

Because of the problems with drug residues and residue testing, there is more motivation than ever to critically evaluate the efficacy of antimicrobial treatments. Intramammary gentamicin was shown to have no effect on duration or severity of experimentally induced *E. coli* mastitis.[25] Routine single intrauterine infusions with procaine penicillin-G or oxytetracycline between days 10 and 21 postpartum in cows diagnosed with endometritis were not efficacious in reducing the cumulative proportion of cows remaining nonpregnant.[26] However, endometritis is still recognized to reduce production, and the ideal treatment is still being pursued. When a study shows a failure of effect of treatment, one can still speculate that a different dose, different route, different frequency of administration or some other parameter might have made the difference. And while the value of antimicrobial treatment of cows with more localized uterine infections seems to be debatable, it is still recommended that systemically ill cows receive antibiotics, fluids, and antiinflammatory drugs.[16,27]

Non-antibiotic alternatives are being widely evaluated for treatment of mastitis and metritis. Scientific evidence for benefit of treating mild cases of mastitis is said to be lacking.[28] Most intramammary treatments are for Gram positive organisms and so may not be logical in herds where Gram negative organisms are the primary problem. Treatments of reproductive tract infections generally compare prostaglandin to antimicrobials. In cows with retained fetal membranes, cows treated with fenprostalene or 5g of IU oxytetracycline daily until one day after the membranes were expelled were compared. Cows treated with fenprostalene had more pyrexia, more metritis at 10-24 days postpartum, and expelled the membranes an average of one day sooner compared to cows treated with oxytetracycline. However, there were no significant differences in the percentage pregnant, days open, or services per conception.[27] In a small study with cows that were not identi-

fied as having metritis until 9-23 days postpartum, 3 days of 3 g oxytetracycline IU was compared to 3 days of prostaglandin or no treatment. Fewer cows treated with oxytetracycline had purulent discharge or positive uterine cultures 2 weeks after their initial examinations.[29] However, subsequent reproductive parameters were not significantly different, although the numbers of cows in each group was small.

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