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Milk Antimicrobial Residues in Holstein Dairy Cattle Treated for Toxic Puerperal Metritis

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Abstract

The objective of this study was to determine the presence of antimicrobial agents in milk and the time milk from cows treated for toxic puerperal metritis remained positive for antimicrobial residues. Fifty-one Holstein dairy cows were divided into three treatment groups: Group 1 was treated with penicillin; Group 2 was treated with penicillin and tetracycline; and Group 3 was treated with ceftiofur sodium. Cows in Groups 1 and 2 received a daily intramuscular injection of procaine penicillin G at the standard farm-wide dose of 18 million units for five consecutive days, nearly four times the recommended dose of 3000 U/lb (6600 U/kg). In addition, cows in Group 2 were infused with 6 g of oxytetracycline diluted in 75 ml of sterile water on days 1, 3 and 5. Cows in Group 3 received a daily intramuscular injection of ceftiofur sodium at a standard farm-wide dose of 1 g for five consecutive days. Milk samples were collected on day 1, before the first dose of antimicrobial agent was administered, and on days 6 through 12 after the final day of treatment with antimicrobial agents. LacTek™ B-L (beta-lactam), LacTek™ TC (tetracycline), and LacTek™ CEF (ceftiofur) test kits were used to determine penicillin, tetracycline and ceftiofur sodium residues, respectively, in milk samples. All three test kits used in this study have been phased out of production and are no longer available. Milk from 9 of 17 cows treated with penicillin was positive for beta-lactam residues for an average of 3.44 days post-treatment. In a separate group, 6 of 17 cows treated with penicillin were positive for beta-lactam residues for an average of 3.66 days post-treatment. Nine of 17 cows treated with oxytetracycline were positive for tetracycline residues for an average of 1.22 days following treatment. No milk residues were detected in cows treated with ceftiofur sodium. Overall, antimicrobial residues were found in milk from cows treated with penicillin and oxytetracycline for 1 to 7 and 0 to 3 days, respectively, from the last day of treatment. In this study, milk from cows treated with penicillin tested positive for residues longer than expected and longer than the labeled withholding time. Antimicrobial screening may be necessary to prevent food contamination.

Résumé

L'objectif de cette étude était d'évaluer la présence d'agents antimicrobiens dans le lait et de déterminer la durée de la période pendant laquelle le lait de vaches traitées pour la métrite toxique puerpérale affichait la présence de résidus antimicrobiens. Un total de 51 vaches laitières Holstein a été divisé en trois groupes recevant des traitements différents : le groupe 1 recevait de la pénicilline, le groupe 2 était traité avec de la pénicilline et de la tétracycline tandis que le groupe 3 était traité avec du ceftiofur de sodium. Les vaches des groupes 1 et 2 recevaient une injection intramusculaire journalière de procaïne pénicilline G, à la dose de 18 millions d'unités normalement utilisée à la ferme, pendant cinq jours consécutifs ce qui représente une dose près de quatre fois plus élevée que la dose recommandée de 3000 U/lb (6600 U/kg). Les vaches du groupe 2 recevaient en plus par infusion 6 g d'oxytétracycline diluée dans 75 ml d'eau distillé pendant les jours 1, 3 et 5. Les vaches du groupe 3 recevaient une injection intramusculaire journalière de ceftiofur de sodium, à la dose de 1 g normalement utilisée à la ferme, pendant cinq jours consécutifs. Des échantillons de lait étaient recueillis au jour 1, avant l'administration de la première dose d'agent antimicrobien, et durant la période de 6 à 12 jours suivant le dernier jour de traitement. Les trousses de tests LacTek™ B-L (bêtalactamine), LacTek™ TC (tétracycline) et LacTek™ CEF (ceftiofur)

ont été utilisées pour confirmer respectivement la présence de résidus de pénicilline, de tétracycline et de ceftiofur dans les échantillons de lait. Ces trois trousses de tests ne sont maintenant plus disponibles commercialement. Le lait de neuf des 17 vaches traitées avec la pénicilline avait des signes résiduelles de bêtalactamine pendant 3.44 jours en moyenne suite au traitement. Dans un autre groupe, le lait de six des 17 vaches traités avec la pénicilline avait des signes positifs de résidus de bêtalactamine pendant une période moyenne de 3.66 jours suite au traitement. Le lait de neuf des 17 vaches traitées avec l'oxytétracycline avait des signes résiduelles de tétracycline pendant 1.22 jours en moyenne suite au traitement. Aucun résidu n'a été détecté dans le lait des vaches traitées avec le ceftiofur de sodium. Globalement, des résidus antimicrobiens se retrouvaient dans le lait des vaches traitées avec la pénicilline du jour 1 au jour 7 post-traitement et du jour 0 au jour 3 post-traitement pour l'oxytétracycline. Dans cette étude, le lait des vaches traitées avec la pénicilline a testé positif pour des résidus plus longtemps que prévu et plus longtemps que le temps de retrait recommandé. Le dépistage antimicrobien pourrait être nécessaire pour prévenir la contamination des aliments.

Introduction

Treatment of dairy cattle for uterine infection with antimicrobial agents can result in residues in milk.[7,8] The Food and Drug Administration (FDA) has established "safe levels" for residues of antimicrobial agents. Safe levels are not the official tolerance levels established for animal drugs under the Federal Food, Drug and Cosmetic Act, but rather, the FDA established "safe levels" as a guide for deciding whether or not to prosecute producers whose milk contains antimicrobial residues. Milk must be discarded if the antimicrobial residue screening test results are positive, which indicates that drug levels are higher than the FDA-established "safe levels." Positive screening tests could indicate a violation of food safety because the resultant residues could theoretically promote the emergence of bacterial resistance or pose a risk to human health.

The risk to human health from antimicrobial residues appears low. It is not likely that human enteric flora will develop resistance to antimicrobials due to prolonged consumption of small quantities of antimicrobial agents.[1] Bacteria are not likely to acquire resistance during growth in adulterated milk because of pasteurization.[1]

Estimates indicate up to 10% of people may be allergic to penicillin or its metabolites.[22,26] Penicillin may cause hypersensitivity or stimulate allergic responses in sensitized people, however, the risk of a hypersensitivity reaction following the consumption of adulterated milk is very low. Only one of six reported cases of adverse drug reactions was confirmed to be an allergic reaction to penicillin in milk.[1,10,26] Previously sensitized individuals are more at risk when consuming adulterated milk.[1] Other drugs known to cause allergic reactions include cephalosporins, tetracyclines and aminoglycosides, but no reported cases have been attributed to residues in milk.[1,26]

The occurrence of beta-lactam residues in milk has steadily declined from about 13% prior to 1962, to less than 0.5% in 1971 and to about 0.001% in 1997.[25,26] The Milk Marketing Board of the United Kingdom surveyed producers and found that intramammary therapy was responsible for 61% of failed residue tests, dry cow therapy contributed 31%, systemic therapy contributed 6% and other causes accounted for 1%.[1,10]

The causes for adulteration of milk or meat with antimicrobial residues are many, including failure to observe withdrawal times, failure to identify treated animals and extra-label use of drugs. A retrospective review of inspection reports revealed failure to observe withdrawal times (61%), use of unapproved drugs (10%), consumption of milk or colostrum by calves from medicated cows (9%), lack of medical records (6%) and exceeding recommended doses (6%) as the five most common causes of residues.[26]

In the United States, the annual expense of testing and the cost of discarding antimicrobial adulterated milk are more than 20 million dollars.[17] Testing for antimicrobial residues in milk has shown that 99.9% of farm milk (milk tankers or producer samples) is free of antimicrobial residues, and the use of currently available screening kits helps prevent antimicrobial adulteration of milk.[17,23,25] Although quality assurance programs have been designed for producers and veterinarians to work closely together to ensure antimicrobial residues are eliminated from the food supply, limited residue information is available on commonly used extra-label antimicrobial agents to assist the veterinarian in formulating quality assurance plans. The objective of this study was to determine the presence of antimicrobial agents in milk and the length of time milk from cows treated for toxic puerperal metritis remained positive for antimicrobial residues. Cows were treated with antimicrobial agents at dosages routinely used by dairy veterinarians.

Materials and Methods

Animals

Fifty-one Holstein cows from a 3500-cow dairy in north central Florida were diagnosed with toxic puerperal metritis and treated with antimicrobials. Cows were housed in a separate hospital facility on the farm. The two main criteria used to diagnose toxic puerperal

metritis in these cows were an elevated rectal temperature and a foul-smelling, watery uterine discharge. Other criteria used to aid in the diagnosis included decreased milk production, decreased appetite and general appearance of the animal.

Treatment

The animals were part of a research project studying the effect of three different antimicrobial treatments on cows with toxic puerperal metritis in which no statistically significant results attributable to the treatments had been observed.[24] Cows were randomly assigned to the treatment groups; Groups 1 and 2 received a daily intramuscular injection of procaine penicillin G[a] at a standard farm-wide dose of 18 million units for five consecutive days, nearly four times the recommended dose of 3000 U/lb; (6600 U/kg). In addition, cows in Group 2 received an intrauterine infusion of 6 g of oxytetracycline[b] diluted in 75 ml of sterile water[c] on days 1, 3 and 5. Cows in Group 3 were treated with a daily intramuscular injection of 1g of ceftiofur sodium[d] for five consecutive days. At the time this project was conducted, ceftiofur sodium was administered according to the recommended dose, but it was not labeled for treatment of metritis. Ceftiofur hydrochloride,[e] a sister product to ceftiofur sodium, is now labeled for treatment of metritis. All intramuscular injections were administered in the neck, low semimembranosus or semitendinosus muscles. There was no untreated control group.

Measured variables

Milk samples – Composite milk samples consisting of equal volumes of foremilk from all four quarters of each cow were used for testing. Milk samples were collected into milk culture vials on day 1, before the first dose of antimicrobial was administered, and on days 6 through 12 after the final day of treatment with antimicrobial agents. Milk samples were stored frozen at -6.7°C.

Antimicrobial residue analysis

Antimicrobial residues were determined by the use of enzyme-linked immunosorbent assays on milk samples. LacTek™ B-L (beta-lactam), LacTek™ TC (tetracycline) and LacTek™ CEF (ceftiofur) test kits were used to determine penicillin, tetracycline and ceftiofur residues in treated cows. These three test kits have been phased out of production and are no longer available. Table 1 lists the kits, sensitivity values and safe/tolerance levels of the antimicrobial agents used in this study. The same testing procedures were used for all three test kits. The kits were brought to room temperature of 68 to 72° F (20 to 22° C) before beginning the assays and remained at room temperature during use. Test tubes were placed in a rack and labeled according to cow number and day of sample collection. The first tube was labeled "positive standard," and a standard was done for every testing period. A 250 µl volume of standard solution[f] was added to the test tube labeled "standard." A 250 µl volume of milk was pipetted and slowly added directly to the bottom of the sample tubes to avoid excess foam. Immediately after milk was added, a 250 µl volume of tracer solution[f] was added to the bottom of the standard test tube and all milk sample test tubes. Tubes were incubated and agitated for three minutes at room temperature. At the end of the incubation period, tubes were drained and washed five times with deionized water. All of the wash solution and residual moisture was shaken from the tubes and 500 µl of color developer solution[f] was added to each tube. Tubes were incubated and agitated for three minutes at room temperature. Immediately after incubation, 500 µl of stop solution[f] was forcefully added to each tube. Each tube was read immediately after adding the stop solution by using the automatic reader/printer[f] in the 0.9 ratio mode. Positive or negative results were displayed and recorded for each sample.

Table 1. Antimicrobial drug residue detection test kits, sensitivity values, and safe/tolerance levels for antimicrobial agents.

Residues	Kit[1]	Safe/tolerance Levels (ppb)[2]	Sensitivity (ppb)[3]
Penicillin	LacTek™ B-L	5	5
Tetracycline	LacTek™ TC	300	30
Ceftiofur	LacTek™ CEF	300	50

[1]Manufactured by Idetek, Inc., Sunnyvale, CA. Test kits are no longer manufactured

[2]Current levels established by Food and Drug Administration determined to be safe or tolerant

[3]Limits of detection during time of this study (October 1995)

Results

Fifty-one cows divided into three treatment groups were included in the clinical trial; there were 17 cows in each treatment group. To be eligible for antimicrobial residue analysis, cows had to be negative for residues on day 1, which was prior to the initial treatment, and have a negative result during the sampling period (day 6 through day 12). Milk samples that were positive for the entire sampling period (day 6 through day 12) after the last day of treatment were not included in the analysis.

Nine of 17 cows in Group 1 and 6 of 17 cows in Group 2 were eligible for antimicrobial residue analysis. A total of eight cows (Group 1 = 4; Group 2 = 4) tested positive for beta-lactam residues during the entire sampling period (day 6 through day 12). Therefore,

these animals were not included in the analysis because the exact time for clearance was not known for these eight cows.

Table 2 shows descriptive data for antimicrobial residues for each treatment group. For cows in Group 1, beta-lactam residues were detected in milk for an average of 3.44 days and a median of 4 days. For those in Group 2, beta-lactam residues were present for an average of 3.66 days and a median of 3.5 days. The minimum number of days from the final day of treatment (Group 1 = 1 and Group 2 = 2) and the maximum number of days from the final day of treatment (Group 1 = 6 and Group 2 = 6) for eligible cows were determined for beta-lactam residues.

Nine of 17 cows in Group 2 tested negative for tetracycline residues on day 1 prior to treatment, and were eligible for antimicrobial residue analysis. As shown in Table 2, the average number of days with tetracycline residues was 1.22 and the median number of days was 1. The minimum number of days from the last day of treatment was 0 and the maximum number of days from the final day of treatment was 3 for cows testing positive for tetracycline residues.

All 17 cows in Group 3 tested negative for ceftiofur on day 1 prior to treatment and were eligible for antimicrobial residue analysis. As shown in Table 2, all 17 cows tested negative on day 6, which was the first sample taken after the last day of treatment.

Discussion

This study compared antimicrobial residues in milk from cows diagnosed and treated for toxic puerperal metritis by using three different antimicrobial agents or combination of antimicrobial agents commonly used by dairy veterinarians. Antimicrobial residues occur in milk of cows treated either by intramuscular injection or by intrauterine infusion.[8,12,17,21] Systemic penicillin is currently one of the treatment choices recommended for the treatment of toxic puerperal metritis.[13,18,20] In cattle, procaine penicillin G is labeled only for treatment of bacterial pneumonia caused by *Pasteurella multocida*, at a dose of 3000 U/lb (6600 U/kg) of body weight administered intramuscularly once daily.[5] The labeled dose is markedly less than the dose currently being used to treat toxic puerperal metritis.

The mean number of days cows in Groups 1 and 2 tested positive for beta-lactam residues post-treatment was 3.44 and 3.66 days, respectively, and the median number of days was 4 and 3.5 days, respectively. These results provide veterinarians and producers with valuable information which could allow them to make more informed decisions on how to use and monitor certain antimicrobial agents. Also, when using an antimicrobial screening test, it may be feasible to wait until four days after the last day of treatment with penicillin to start testing. The extended period of time antimicrobial residues were detected in this trial was likely due to the extra-label dose of antimicrobial agents used. In addition, reduced milk production due to toxic puerperal metritis could have contributed to the prolonged clearance time for penicillin. Booth and Harding[10] reported that high producing cows (> 55 lb [25 kg]/day) had residues for a shorter period of time than cows with medium (33 to 44 lb [15 to 20 kg]/day) or low (< 33 lb [15 kg]/day) milk production.

The recommended milk withholding time for procaine penicillin G administered at the labeled dose is 48 hours from the last treatment.[5] The Food Animal Residue Avoidance Databank (FARAD) recommends a 96-hour milk withholding time when cows are treated intramuscularly at a dose of 9545 U/lb (21,000 U/kg) of body weight SID, not to exceed 5 days of treatment and 10-15 ml per injection site.[19] In this study, procaine penicillin given at a dose of 60 ml (18 million units) resulted in antimicrobial residue times ranging from 1 to 7 days, but could have been longer than 7 days if more milk samples were taken after treatment ended. A total of eight cows tested positive for penicillin on day 12, which was the final day milk samples were taken. The variability in the time cows remained positive for penicillin residues is interesting. Although the average number

Table 2. Mean, median, minimum, and maximum number of days for antimicrobial residues for each treatment group for cows eligible for antimicrobial agent analysis.

	Treatment[1]	N	Mean	Median	Minimum	Maximum[2]
Group 1	Penicillin	9	3.44	4	1	6
Group 2	Penicillin	6	3.66	3.5	2	6
	Oxytetracycline	9	1.22	1	0	3
Group 3	Ceftiofur sodium	17	0	0	0	0

[1]Group 1 = intramuscular procaine penicillin G; Group 2 = intramuscular procaine penicillin G plus intrauterine oxytetracycline; Group 3 = intramuscular ceftiofur sodium

[2]Samples were only taken for 7 days from the last day of treatment

of days was calculated for cows testing positive for beta-lactam residues, this average did not include the group of cows that tested positive on the day the final milk sample was taken. Therefore, the averages calculated in this study could be skewed. The averages could also be different if all cattle were included in the analysis. It appears longer withholding times may be necessary for cows treated with extra-label dosages of penicillin. Another option is to do individual milk screening tests on these cows. If individual cows are not screened, then a screening test should be performed on bulk tank milk.

Reliable milk antimicrobial residue test kits are useful tools to avoid adulterating the food supply. Residue screening kits are not without problems, and their use can result in false positive or false violative results.[11,12,15,22] A false positive results when a test indicates there are antimicrobial agents present when in fact there are no antimicrobial agents present. False violative results occur when antimicrobial screening tests show that a milk sample is positive for an antimicrobial agent but the test sensitivity is lower than the legal "safe level" or "safe tolerance" established by the FDA. Therefore the sample is not adulterated but the test says it is. These false results may cause the producer to discard non-adulterated milk, resulting in a loss of revenue. A 16% rate of false-positive results has been reported when using antimicrobial tests that rely on microbial inhibition.[15] Several different compounds produced by animals suffering from bacterial infections can affect the reliability of milk antimicrobial test kits. Cullor *et al*[11] demonstrated that, with the exception of LacTek™ beta-lactam assay, a high level of false positive results is found when using milk antimicrobial test kits. LacTek™ assays were used to detect antimicrobial agents in this study. Even with the reported problems seen with milk residue kits, they are still used by producers to identify milk residues from animals treated for various diseases, and currently may be the best available tool to prevent adulteration of the food supply.[1,10]

Intrauterine infusion with oxytetracycline is commonly recommended by veterinarians for the treatment of toxic puerperal metritis.[18,21] Intrauterine infusion of various antimicrobial agents leads to milk residues, and tetracycline, penicillin and chloramphenicol residues have been found in milk after intrauterine infusion.[7,8] However, disagreements exist over whether milk residues occur after intrauterine infusion with tetracyclines.

Bierschwal and Uren[6] were the first to demonstrate absorption of tetracyclines by the bovine uterus. They concluded that chlortetracycline was rapidly absorbed from the uterus, and peak serum levels were attained by two hours after infusion. Several researchers who infused different treatment dosages of oxytetracycline saw mixed results. Anderson *et al*[2] infused the uterus of cows with 2 g of oxytetracycline diluted in 500 ml of saline, and five of six cows had milk oxytetracycline levels below the FDA safe value of 30 ppb by eight milkings (96 hours). Since the publication of Anderson's research, the FDA has established a safe value of 300 ppb for oxytetracycline or the sum of all tetracyclines present.[9] Dinsmore *et al*[12] showed similar results after infusing cows with retained fetal membranes with 5 g of oxytetracycline. They concluded that significant residues remained in milk after treatment. The duration of residues ranged from 0 to 144 hours, with a mean of 48 hours after the last infusion. Kaneene *et al*[16] showed similar results when they infused cows with 3 g of oxytetracycline and found residues ranging from 12.5 to 44 hours after the last treatment, with a mean of 26.6 hours.

Oxytetracycline is labeled for lactating dairy cattle for treatment of several diseases caused by a wide variety of organisms. It is labeled for intramuscular, subcutaneous or intravenous administration at 3 to 5 mg/lb (6.6 to 11 mg/kg) of body weight once daily.[4] It is not labeled for intrauterine administration. The recommended milk withhold time for tetracycline is 96 hours when used according to label. Oxytetracycline residues in this study were detected for an average of 1.22 days, the time which is in agreement with other reports.[2,12,16] These results demonstrate that failure to withhold milk after intrauterine treatment results in a high probability of residue violation. The variability seen in residue times is further indication for need of residue testing.

Ceftiofur sodium is labeled for interdigital pododermatitis and bovine respiratory disease associated with a variety of organisms at an intramuscular dose of 0.5 to 1.0 mg/lb (1.1 to 2.2 mg/kg) of body weight once a day.[3] There is no meat or milk withholding time for ceftiofur sodium when used according to label directions. Ceftiofur sodium is currently not labeled for the treatment of metritis in lactating dairy cattle, however, ceftiofur hydrochloride is. Ceftiofur sodium could be a useful treatment for toxic puerperal metritis because of the zero withholding time and efficacy against many of the organisms causing the disease. The FDA has established the legal "safe level" of "parent" ceftiofur sodium in milk at 50 ppb,[9] however, no parent drug is found in the milk when used according to the label. The level of 50 ppb is used to protect against the "extra-label" use of ceftiofur sodium. Research by Jaglan *et al*[14] showed that the use of ceftiofur sodium in dairy cattle in accordance with label directions does not result in residues higher than the legal limit. They also found that tests using microbial inhibition or receptor binding gave positive test results for milk samples.

In this study, no ceftiofur sodium residues were detected. Once administered, ceftiofur sodium becomes metabolized to desfuroylceftiofur, which later is metabolized to desfuroylceftiofur cysteine disulfide,

desfuroylceftiofur disulfide and desfuroylceftiofur-protein.[14] These metabolites are present in milk, the majority of which are bound to milk protein and are therefore inactive. A portion of the remaining unbound metabolites has also been found to be microbiologically inactive. A proportion of free metabolites is microbiologically active, but the level is very low and below the detection limits of most screening tests. The residue test results in this study are in agreement with others.[14]

Conclusions

The potential for antimicrobial residues in the food supply is a serious concern. Dairy veterinarians commonly use beta-lactams, tetracyclines and cephalosporins to treat infectious diseases of dairy cattle. The use of penicillin at extra-label doses dictates longer milk withhold times than found on the label. The average milk-withhold time determined in this study was derived from animals for which an endpoint could be determined, but these values in no way should be extrapolated to a dairy owner's quality assurance program for residue prevention. These values could be longer if a negative residue outcome could have been determined for all animals. When oxytetracycline is infused into the uterus of dairy cattle, milk residues will occur. Results of this study revealed variability in the number of days from the last treatment that cows remained positive for both penicillin and tetracycline. This variability suggests the need to test milk from cows treated with antimicrobials with approved residue screening kits, especially when using drugs in an extra-label manner. If individual cows treated in an extra-label manner are not tested, then at a minimum, bulk tank milk should be tested. Also, this study provides information to the dairy industry regarding what day residue testing should begin after treatment, therefore veterinarians and producers can make more informed decisions about testing protocols and antimicrobial selection.

Footnotes

[a]Pen-Aqueous, AgriPharm, Memphis, TN
[b]Oxy-Mycin 100, AgriPharm, Memphis, TN
[c]Sterile Water, Abbott Laboratories, North Chicago, IL
[d]Naxcel, Pharmacia Animal Health, Kalamazoo, MI
[e]Excenel, Pharmacia Animal Health, Kalamazoo, MI
[f]LacTek, Idetek, Inc., Sunnyvale, CA

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