

Relationship between uterine pathology and depletion of oxytetracycline concentrations in plasma and milk after intrauterine infusion

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Introduction

Up to 90% of dairy cows develop bacterial contamination of the uterus during the first week after calving. Intrauterine treatment with antimicrobials is commonly practiced on dairy farms, even though studies demonstrating improved reproductive performance after treatment are lacking. Intrauterine infusion of antimicrobials can result in costly milk discard, and increases the risk for antimicrobial residue in bulk-tank milk intended for human consumption. Because there are currently no antimicrobials approved for intrauterine administration in cattle, the veterinarian is primarily responsible for ensuring that milk from treated cows is free from antimicrobial residues. Results of previous trials have indicated considerable variation in the depletion profile of drugs after intrauterine infusion. For this study, we hypothesized that the variability in the elimination of oxytetracycline in milk is associated with the extent of uterine pathology among cases.

Materials and Methods

Nine Holstein cows with mild to severe endometritis were administered 4 grams of oxytetracycline by uterine infusion. Milk samples were collected twice daily at milking for 7 days after treatment to determine oxytetracycline concentration. Blood samples to determine circulating oxytetracycline concentration were collected immediately after infusion, and once daily for 7 days. Endometritis scores were assigned to each cow by use of a previously described scoring system on the basis of appearance and volume of the uterine discharge. Plasma and milk samples were frozen after collection and transported to the laboratory for analysis. Oxytetracycline concentrations in milk were extracted into acetonitrile and cleaned up by solid phase extraction (SPE). Oxytetracycline concentrations in plasma were prepared by protein precipitation with trichloroacetic acid (TCA). Concentrations were then quantified by liquid chromatography-mass spectrometry (LC-MS/MS). Oxytetracycline concentrations in plasma and milk over time were compared by non-compartmental analysis by means of a commercial software program

(Kinetica, Thermo Scientific, Philadelphia, PA). Plasma and milk pharmacokinetic parameters were then compared with endometritis scores by use of a statistical screening tool (JMP 10.00, SAS Institute, Cary, NC).

Results

The C_{max} of oxytetracycline in plasma (mean ± SEM, 0.23 ± 0.05 µg/mL; 95% confidence interval [CI], 0.11 to 0.35 µg/mL) was recorded at 24 hours after intrauterine infusion. The mean ± SEM plasma elimination half-life of oxytetracycline after intrauterine infusion was 21.68 ± 11.16 hours (95% CI, 13.1 to 30.3 hours). The C_{max} of oxytetracycline in milk (mean ± SEM, 0.20 ± 0.06 µg/mL; 95% CI, 0.05 to 0.35 µg/mL) was recorded at 37 hours after intrauterine infusion. The mean ± SEM milk elimination half-life of oxytetracycline after intrauterine infusion was 12.03 ± 0.99 hours (95% CI, 9.76 to 14.30 hours). Greater uterine pathology scores at the start of treatment tended to be positively associated with higher maximum oxytetracycline concentrations in milk ($R^2 = 0.30$; $P = 0.13$) and larger areas under the extrapolated milk oxytetracycline concentration vs. time curve ($R^2 = 0.64$; $P = 0.0089$). Cows with higher average uterine pathology scores also had higher oxytetracycline concentrations in last milk sample collected than did cows with low average uterine pathology scores ($R^2 = 0.63$; $P = 0.03$).

Significance

Results suggested that cows with greater uterine pathology scores tended to absorb and eliminate more oxytetracycline from the uterus than did cows with lower uterine pathology scores. We surmise that this effect may be caused by increased blood flow to the uterus associated with the inflammatory process that increases the rate and extent of drug absorption following intrauterine infusion. These findings will assist practitioners in determining appropriate milk withdrawal periods for commonly infused antimicrobials in dairy cows. This is especially critical, given that tests for detecting antimicrobial residues in milk have become more sensitive.