PHARMACOKINETICS OF CEPHAPIRIN SODIUM IN MILK USING AN 8-DAY EXTENDED THERAPY PROGRAM OF DAILY INTRAMAMMARY INFUSION IN HEALTHY LACTATING HOLSTEIN-FRIESIAN COWS

Patrick J. Gorden1, Mark van der List2, Fred D. Lehman2, Robert K. Lantz3, Peter D. Constable4

1Iowa State University, Ames, Iowa, USA 2Boehringer-Ingelheim LLC, St. Joseph, Missouri, USA 3Rocky Mountain Instrumental Laboratories, Fort Collins, Colorado, USA 4Purdue University, West Lafayette, Indiana, USA

Introduction
Cephapirin (CEPH) is a frequently administered intramammary (IMM) treatment for clinical mastitis in the U.S. (Sawant et al., 2005; Pol and Ruegg, 2007; USDA, 2009). The current label claim for IMM CEPH (200 mg) is 2 treatments 12 h apart with 96 h of milk withhold after the last treatment. A large percentage of dairy farms milk cows three times per day (3X) making 12 h IMM treatment intervals impractical. Additionally, to reduce residue risk, many dairy farmers desire to administer IMM therapy one time per day when hospital personnel are present.

General therapeutic principles are to administer antimicrobials for at least 48 h past the resolution of clinical signs. For the treatment of clinical mastitis, the general therapeutic principal suggests that it may be therapeutically beneficial to treat for a longer period of time than the label recommendation. Extended therapy with an IMM antimicrobial has increased the microbiological cure rate for clinical mastitis episodes due to Strep uberis (Krömker et al., 2010) and subclinical mastitis episodes due to Staph aureus, Strep uberis, environmental Strep, and Coagulobacterium bovis (Oliver et al., 2004; Deluyker et al., 2005; Roy et al., 2009).

The objective of this study was to determine the pharmacokinetics of extended, one-time/day therapy with IMM CEPH in lactating dairy cattle milked 3X.

Materials and Methods
Eight healthy Holstein-Friesian cows were administered CEPH (200 mg) into all 4 mammary glands every 24 h after milking. Cows were milked three times per day (3X) and concentrations of CEPH and desacetylcephapirin were determined in bucket milk (the total volume of milk collected via the glands every 24 h after milking. Cows were milked three 3X and concentrations of CEPH and desacetylcephapirin were determined in bucket milk (the total volume of milk collected via the glands every 24 h after milking. Cows were milked three times per day (3X) making 12 h IMM treatment intervals impractical. Additionally, to reduce residue risk, many dairy farmers desire to administer IMM therapy one time per day when hospital personnel are present.

Results and Discussion
The maximum CEPH concentration was 128 ± 57 µg/mL (mean ± SD), the elimination rate constant from the central compartment (k10) was 0.278 ± 0.046 (1/h), clearance was 0.053 ± 0.023 L/h, the half time for elimination (1/2) was 2.55 ± 0.40 h, and the mean residence time was 2.65 ± 0.79 h. The pharmacokinetic values were consistent with those expected following IMM infusion of water soluble, charged, poorly lipid soluble antimicrobial agents. The CEPH concentration was below the approved tolerance in all cows by 96 h after the last infusion, which is the labeled withholding time for the preparation used. Extended therapy for 8 days provided milk CEPH concentrations above the MIC for common Gram-positive mastitis pathogens (0.1 to 1.0 µg/mL) for the duration of therapy and for an additional 16 to 32 h after the end of treatment.

Conclusions
Our findings suggest that IMM CEPH could be administered at a 24 h interval for up to 8 days in cows milked 3X with no significant effect on residue levels by 96 hours after the last treatment. Longer withdrawal times would be prudent for cows with mastitis or low milk production. Additionally, as with any extra label use of IMM formulations, cowside residue testing would be advised. Further investigation is needed to determine the effect of extended therapy using daily IMM administration of CEPH on treatment efficacy and pharmacokinetics in lactating dairy cows with clinical mastitis.

References

Acknowledgements:
This study was supported, in part, by a grant from Boehringer Ingelheim Vetmedica, Inc.