

# Pharmacokinetics of hetacillin in dairy cattle following 3X milking

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## Introduction

Mastitis remains a critical disease in the dairy industry and the use of intramammary antibiotics plays a critical role in mastitis treatment. Hetacin-K® (Boehringer Ingelheim Vetmedica, Inc) is currently approved as an intramammary antibiotic that is used to treat mastitis in dairy cows. It is approved for once daily intramammary administration and can be used for a total of three days. More and more dairy farms are milking three times per day instead of the traditional two times per day; however, there is very little pharmacokinetic data on the use of intramammary drugs such as Hetacin-K® in a 3X system. The purpose of this study was to determine if once daily intramammary infusion of Hetacin-K® is sufficient to maintain therapeutic drug concentrations in cattle milked three times per day.

## Materials and Methods

Eight Holstein cattle being milked 3X per day were used in this study. Each cow was in mid to late lactation, had not been treated for mastitis during their present lactation and was milking between 50 and 75 pounds per day. After collecting a baseline milk sample, each cow received intramammary infusions of Hetacin-K® in the left front and right rear quarters once daily for three days according to label directions. Composite samples representing milk from each of the treated quarters were collected at each milking and frozen until analysis. Milk was collected for an additional three days following completion of the intramammary infusions to model the elimination phase of hetacillin excretion. When administered as an aqueous solution, hetacillin is rapidly converted back to ampicillin and acetone. Milk samples were therefore analyzed for ampicillin concentrations using a UPLC method.

## Results

The mean concentration of ampicillin from treated quarters after intramammary administration on days 1 thru 3 was  $6.98 \pm 2.81$  µg/mL,  $0.48 \pm 0.22$  µg/mL and  $0.016 \pm 0.008$  µg/mL at 8, 16 and 24 hours after infusion, respectively and immediately prior to the next treatment. All quarters had antibiotic concentrations well above the minimum inhibitory concentration of 0.25 µg/mL at 8 hours post-infusion and most quarters had concentrations  $\geq 0.25$  µg/mL at the 16 hour milking. Milk concentrations had fallen well below the MIC by the 24 hour period immediately prior to the next infusion. All 8 cows in this study consistently had individual quarter milk ampicillin concentrations below the FDA tolerance of 10 ppb within 24 hours of the last infusion. This is significantly faster than the current withdrawal time of 72 hours and suggests more frequent milking might result in faster elimination of the drug from the udder.

## Significance

When creating dosing regimens for beta-lactam antibiotics, it is generally accepted that concentrations in the blood or target tissue should be above the MIC for 50-60% of the dosing interval in patients that are not immunocompromised. Based on this study, milk ampicillin concentrations are above the MIC<sub>90</sub> of 0.25 µg/mL for at least 14 to 16 hours in dairy cows milked three times per day. When Hetacin-K® is used every 24 hours as per the label directions, ampicillin concentrations exceed the MIC for 60-67% of the dosing interval in most cases. Therefore Hetacin-K® should be an effective treatment for the vast majority of Gram-positive mastitis pathogens when used according to label directions in cows milked three times per day.