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Altered plasma pharmacokinetics of ceftiofur hydrochloride in cows affected with severe clinical mastitis

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ABSTRACT

Mastitis is a frequent problem among dairy cows, reducing milk yield and increasing cull rates. Systemic therapy with the cephalosporin antimicrobial ceftiofur hydrochloride (CEF) may improve therapeutic outcomes, but the incidence of CEF violative residues has increased annually since 2011. One potential explanation is that disease status may alter the pharmacokinetics (PK) of CEF. To test this hypothesis, we compared the plasma PK of CEF in healthy cows with those with severe endotoxic mastitis. Eight cows with naturally occurring mastitis and 8 clinically healthy cows were treated with 2.2 mg of CEF per kilogram of body weight once daily for 5 d via the intramuscular route. Blood was collected at 0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 8, 16, and 24 h after the first CEF administration and every 8 h thereafter until 120 h after the final dose. Plasma samples were analyzed for CEF concentrations using liquid chromatography coupled with mass spectrometry. With the exception of time 0, CEF was detected at all time points. The disease group had a significantly higher plasma CEF concentration at $t = 3$ h after the first injection and a significantly lower plasma concentration from 40 to 152 h following the first injection, with the exception of the $t = 64$ h time point. Data following the first injection (time 0–24 h) were fit to a single-dose, noncompartmental PK model. This model indicated that the disease group had a shorter plasma half-life. A multidose, noncompartmental model was used to determine steady-state PK. Compared with control cows, the disease group had an initially higher peak concentration and a higher volume of distribution and drug clearance rates. The disease group also had a lower area under the curve per dosing interval, steady-state concentration maximum, and dose-adjusted peak steady-state concentration. All other PK parameters were not different between the 2 groups. Altered PK, as suggested by this trial, may contribute to an increased risk for the development of a violative residue in meat. Further research is needed to more completely characterize drug distribution in diseased cattle and to study the effect of coadministration of other drugs on drug distribution.
Key words: bovine mastitis, ceftiofur, pharmacokinetics, drug residue

INTRODUCTION

Mastitis is the most common reason for therapeutic antimicrobial use in dairy cattle, according to the 2007 USDA National Animal Health Monitoring Survey. This survey of the dairy industry in the United States indicated that 18.2% of respondents' cows had been treated for mastitis during the previous 12 mo (USDA, APHIS, 2008). Coliforms are the most common bacterial group causing clinical mastitis, and these infections generally result in more severe infections, with decreased survivability, than other pathogens (Wenz et al., 1998; Erskine et al., 2002; Oliveira et al., 2013).

Reasons for decreased survivability following mastitis include the development of endotoxic conditions with severe intramammary (**IMM**) tissue damage and, potentially, the development of secondary disease. Secondary bacteremia develops in 45% of cows with severe mastitis (Wenz et al., 1998). Systemic ceftiofur (**CEF**) treatment can potentially address severe mastitis and secondary infections. When treated with CEF, fewer cows were sold or died as a result of severe coliform mastitis as compared with cows that were not treated (Erskine et al., 2002). Ceftiofur is a third-generation cephalosporin that is appropriate for use against coliform infections if effective concentrations can be achieved and maintained at the infection site. As a

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result, systemic treatment with CEF, with or without IMM therapy, has been included in many veterinary treatment protocols for moderate or severe clinical mastitis.

Over the past several years, concerns about veterinary drug use have increased, especially around the effect on antimicrobial efficacy in humans and the presence of drug residues in milk and meat. Since fiscal year 2011, violative CEF residues in culled dairy cows from inspector-generated samples have increased more than 5-fold (USDA, FSIS, OPHS, 2013a,b; USDA, FSIS, OPHS, 2014a,b). In 2012 the US Food and Drug Administration (**FDA**) issued a prohibition against extra-label drug use of cephalosporins in bovines (US FDA, 2012). Given the prohibition of a drug so important to the dairy industry, there is clearly a significant regulatory concern about the increase in violative residues. Although the cause of increasing CEF residues is likely multifactorial, one potential explanation may be altered pharmacokinetics (**PK**) and residue depletion of CEF in diseased dairy cattle.

During the drug approval process, sponsoring companies must present the FDA Center for Veterinary Medicine with toxicological and residue depletion studies. Based on these data, the FDA Center for Veterinary Medicine establishes withdrawal periods for meat and milk, if approved for lactating dairy cattle. However, these studies are performed on healthy animals, not animals suffering from infectious diseases (US FDA, 2006a). Because antimicrobials are not intended for healthy animals, data on drug metabolism in diseased animals would provide veterinarians with evidence to more accurately prescribe veterinary drugs and also to better predict residue depletion in these diseased animals. In turn, this could improve treatment efficacy and reduce the risk for violative residues in marketed animals. However, few data from cattle available in the veterinary literature address this topic. The objective of this study was to compare the plasma PK of CEF between healthy dairy cattle and those afflicted with severe clinical mastitis. Our hypothesis was that cows affected with severe infectious disease would have altered CEF PK relative to healthy cows, necessitating variance in dose regimens and withdrawal periods.

MATERIALS AND METHODS

Animals and Eligibility Criteria

This study was completed at the Iowa State University Dairy Farm. The Iowa State University lactating herd consists of approximately 400 animals (approximately 90% Holstein and 10% Jersey), with 365-d rolling herd averages of 11,324 kg of milk, 415 kg of fat, and 357 kg of protein. Throughout the trial, cows were housed in a free-stall barn bedded with recycled manure solids, which is standard practice for this dairy. Cows were fed a TMR and watered ad libitum. Cows were milked 3 times daily at 4 a.m., 12 p.m., and 8 p.m. Cow housing and management met or exceeded the recommendations listed in the *Guide for Care and Use of Agricultural Animals in Research and Teaching* (FASS, 2010). The herd was vaccinated with a J5 core antigen vaccine 42 and 28 d before calving and again 25 and 90 d following calving. The Iowa State University Institutional Animal Use and Care Committee approved the research protocol before commencement of trial procedures (protocol number 6-14-7820-B).

Eight cows that presented with naturally occurring, acute severe toxic clinical mastitis, as described by Wenz et al. (2001), were selected to participate in the trial (disease group). The disease group had a mean (±SD) weight of 607 ± 77 kg (range 453–689 kg). The milking crew of the farm first identified each disease-group cow based on an acute drop in milk production, abnormal milk, and severe swelling in the affected gland. At enrollment, all cows had evidence of systemic clinical signs associated with endotoxemia. To qualify, cows had to present with (1) at least one hot, swollen quarter secreting abnormal milk; (2) an acute decrease in milk production; and (3) evidence of systemic disease involvement determined by the presence of an elevated rectal temperature, depression, dehydration, anorexia, and decreased blood circulation as determined by the presence of congested mucous membranes or delayed capillary refill time.

Upon identification of a disease cow with severe mastitis, a healthy herd mate was matched by breed, DIM, and lactation number to serve as a control. The control group's mean (±SD) weight was 650 ± 100 kg (range 462–751 kg). Disease and control cows were eligible for the trial if they had not been treated with systemic or IMM CEF within the past 20 d and were healthy before enrollment. Furthermore, the cows needed to be 10 or more days from their next scheduled dry period.

Study Design

Disease and control cows were enrolled immediately following the noon milking. Throughout the trial, cows were milked by trial personnel per the farm milking protocol. Prior to the noon milking for the disease-group cows, a milk sample was aseptically collected from the mastitic quarter for bacterial culture. This sample was kept on ice until it was transferred to the laboratory for microbiological analysis.