

Altered Plasma Pharmacokinetics of Ceftiofur Hydrochloride in Cows Affected with Severe Clinical Mastitis

A.S. Leaflet R3086

Patrick J. Gorden, Senior Clinician¹;
Michael D. Kleinhenz, Graduate Assistant¹;
Larry W. Wulf, Laboratory Technician III¹;
Butch KuKanich, Professor²;

Chang J. Lee, Post-Doctoral Research Associate¹;
Chong Wang, Associate Professor¹;
Johann F. Coetzee, Professor¹;

¹Veterinary Diagnostic and Production Animal Medicine,
Iowa State University

²Department of Anatomy and Physiology, Kansas State
University

Summary and Implications

Ceftiofur is the most commonly used antimicrobial in lactating dairy cows. Recently, there has been an increase in the number of violative residues of ceftiofur in the tissues of cull dairy cows. This was the first project in a series of projects we will be completing aimed at characterizing the pharmacokinetics of ceftiofur in disease challenged animals. The results of this study indicate that diseased animals have lower plasma concentrations and altered pharmacokinetics compared to healthy animals. Future work will investigate the influence of altered pharmacokinetics on the presence of violative residues.

Introduction

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 endotoxemic mastitis.

Materials and Methods

Eight cows with naturally occurring mastitis and eight clinically healthy cows were treated with 2.2 mg of ceftiofur hydrochloride/kg of body weight once daily for five days via the intramuscular route. Blood was collected at 0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 8, 16, and 24 hours after the first ceftiofur administration and every eight hours thereafter until 120 hours after the final dose. Plasma samples were analyzed for ceftiofur concentrations using liquid chromatography coupled with mass spectrometry. Ceftiofur concentrations are reported as total ceftiofur, which includes the parent compound and all metabolites. Single dose and

multi-dose non-compartmental pharmacokinetic models were determined for both groups. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC). All PK data are reported as geometric means. Disease and control groups were compared using the Wilcoxon two-sample rank-sum test (Mann-Whitney test). Multiple variables (i. e. drug concentrations and PK values) had distributions that were right skewed with long tails. Therefore, non-parametric methods were used to analyze the data in this situation. Statistical significance was established when $P < 0.05$.

Results and Discussion

Compared to control cows, the disease group had an initially higher peak concentration, 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 two groups.

These data show that significant PK changes occur in diseased animals administered CEF relative to healthy, control animals. These outcomes potentially have public health significance in that: 1) drug efficacy could be lower than expected; 2) there may be an increase in violative drug residues in tissues of cull animals or milk; and 3) this may lead to increases in antimicrobial resistance. This body of evidence suggests that the drug approval process should be changed such that the physiological changes of health-challenged cows are addressed. It does not, however, lead to any conclusions regarding the outcomes of treating health-challenged cows nor the contribution of altered PK on the increasing violative CEF residues found in culled dairy cattle. Further work examining tissue distribution depletion of drugs and their influence on residue levels in diseased animals at the end of their withdrawal periods is necessary to more thoroughly characterize this problem.