Efficacy of Ceftiofur Crystalline Free Acid Administered in the Posterior Aspect of the ear for Treatment of Bovine Respiratory Disease when a Retreatment Moratorium is Imposed

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Objective

The objective of this three-location study was to evaluate the initial and durable cure rates, and to determine the duration of therapy, for ceftiofur crystalline free acid sterile suspension (CCFA-SS) for treatment of bovine respiratory disease (BRD) when a 3, 5 or 7-day retreatment moratorium was imposed. This study tested the hypothesis that retreatment during the period of effective plasma concentrations of ceftiofur may not improve treatment success rates.

Materials and Methods

This multi-location complete block design study was conducted according to the GCP guidelines at three research/commercial feedlots in ID, TX and CO. Crossbred beef cattle (n=1660) were obtained and transported to the research feedlots. Following arrival processing, all cattle were observed by the assigned pen riders. All cattle that met the inclusion criteria (abnormal respiration, depression evident and rectal temperature ≥104.0°F) were randomly assigned to a retreatment moratorium (3, 5 or 7 days following initial treatment) and were administered CCFA-SS (PNU-64279; 200 mg ceftiofur equivalents [CE]/mL) at 3.0 mg CE/lb (6.6 mg CE/kg) BW subcutaneously (SC) in the posterior aspect of the ear. Cattle were returned to the home pen following treatment administration. A total of 781 cattle (mean BW=501 lb) were enrolled.

Pen riders blinded to the assigned treatment groups observed the cattle daily and recorded scores for all cattle that had clinical signs of BRD (or any other disease or injury). Blinding was maintained by having unblinded personnel determine and pull those cattle that were eligible for rectal temperature measurement. Cattle that met the inclusion criteria again on or after the first day they were eligible for retreatment (3, 5 or 7 days after initial treatment, based on randomization) were retreated with CCFA-SS at 3.0 mg CE/lb (6.6 mg CE/kg) BW SC in the posterior aspect of the ear that was not injected at assignment. A five-day moratorium was imposed after retreatment for all cattle, regardless of initial group assignment. Cattle that again met the inclusion criteria five or more days after retreatment were administered standard feedlot therapy (SFLT). At trial A, no further pen rider observations were recorded after an animal was administered SFLT. At trials B and C, pen rider observations continued for all study cattle until 28 days after the last animal in the home pen had been assigned to the study. These differences did not affect analysis of the primary variables.

Data from 765 cattle were included in the analysis. The three decision variables in this study were initial cure rate (percentage of cattle that did not require retreatment on the first day they were eligible), single administration durable cure rate (percentage of cattle that were never retreated) and retreatment durable cure (percentage of cattle that were retreated from the first day allowed through day 9, but never received any additional treatment). Analyses of the proportions of animals that cured within each location-treatment-pen group for each variable were conducted using Freeman-Tukey arcsine transformation. Weighted ANOVA (weights were n+0.5, where n was the number of animals within the location-treatment-pen group) was conducted utilizing the MIXED procedure. The model included the treatment fixed effect and random effects of location, pen within location and residual.

Results

The initial cure rates were 94.1, 92.9 and 96.3% for the 3, 5 and 7 day groups, respectively ($p>0.05$). Single administration durable cure rates were 65.3, 73.2 and 77.3% for the 3, 5 and 7 day groups, respectively. The 7-day group had a significantly higher single administration durable cure rate than the 3-day group ($p<0.05$). The retreatment durable cure rates were 60.1, 59.9 and 69.0% for the 3, 5 and 7-day groups, respec-

tively (p>0.05). ADGs were 2.93, 2.91 and 2.85 lb/day for the 3, 5 and 7-day groups, respectively (p>0.05) for cattle that completed the study. Mortality due to BRD was 1.57, 1.57 and 1.17% for cattle in the 3, 5, and 7-day groups, respectively. Two animals died immediately after CCFA-SS administration. These deaths were determined to be due to inadvertent administration of the formulation into the middle auricular artery. This resulted in retrograde movement of the formulation into the arterial supply of the brain, causing cerebral infarction.

Conclusions

The 12 percentage point increase in the single administration durable cure rate observed with a 7-day retreatment moratorium in this initial non-pivotal GCP multi-location clinical study supports the hypothesis that retreatment based on clinical signs, when therapeutic plasma concentrations of ceftiofur are present (relative to the target pathogens *Mannheimia haemolytica, Pasteurella multocida* and *Haemophilus somnus*), does not improve treatment success rates. These observations provide opportunities to alter the management of BRD and reduce the total number of treatments administered while improving durable cure rates. This study also confirms the necessity for the correct injection technique for this unique formulation and route of administration.

Ceftiofur Crystalline Free Acid Sterile Suspension (CCFA-SS) in Cattle: Pharmacokinetics after Injection in the Middle Third of the Ear and Importance of Injection Technique

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Introduction

Ceftiofur, a time-dependent, bactericidal antibiotic active against bovine respiratory disease pathogens, is effective when the concentrations remain above the minimum inhibitory concentration (MIC) for at least 3-5 days. A new product, CCFA-SS, is a prolonged release formulation of ceftiofur, intended to provide single dose efficacy in cattle. It is administered subcutaneously (SC) in the ear, eliminating any injection in edible tissue. The objective of this study was to generate plasma ceftiofur concentration data following administration of CCFA-SS SC in the middle third of the posterior aspect of the ear.

Materials and Methods

Angus and Angus crossbred beef cattle (n=24; 590-880 lb [270-400 kg]) were administered a single dose of 3.0 mg CE/lb (6.6 mg ceftiofur equivalents ([CE] /kg) BW in the middle one-third of the ear, inserting the needle approximately 1/3 of the length of the ear from the tip, pointed toward the base of the ear. An alternative site is on the rostral third of the caudal surface of the ear. These two locations are parallel to the rostral branch of the middle auricular artery. The needle should be fully inserted, the thumb positioned perpendicular to the needle to allow deposition in the middle third of the ear. Once the full dose is administered, the bleb should be massaged away from the injection site. The consequence of the inadvertent arterial injection could be retrograde delivery of the product to the external carotid artery, which in the bovine continues as the internal carotid artery and is a major blood supply to the brain (this description is in contrast to the description of Sisson and Grossman). Blood samples were collected at 0, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 168 and 240 h after treatment administration. Plasma was harvested and stored at -20∞C before being assayed for ceftiofur and desfuroylceftiofur-related metabolites using the validated HPLC-DCA method. The LOQ of the assay is 0.150 mg CE/mL plasma. The $AUC_{0\text{-}LOQ}$ (by trapezoidal summation) and $t_{>0.2}$ (the time plasma concentrations remained above the therapeutic level of 0.2 mg/mL) were evaluated using the WinNonlin' nonlinear modeling software.