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Dose Determination and Confirmation for Ceftiofur Crystalline-Free Acid Administered in the Posterior Aspect of the Ear for Control and Treatment of Bovine Respiratory Disease

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Abstract

Three studies were conducted to determine and confirm the effective dosage rate of ceftiofur crystalline-free acid sterile suspension (CCFA-SS, 200 mg ceftiofur equivalents [CE]/ml), a long-acting ceftiofur formulation, for control and treatment of bovine respiratory disease (BRD). In each study, CCFA-SS was administered once by subcutaneous (SC) injection in the middle third of the posterior aspect of the ear. Study 1 was conducted using an intratracheal challenge with *Mannheimia* (formerly *Pasteurella) haemolytica* and dosages ranging from 0 to 8.8 mg CE/kg to select a dosage for further field testing. In Study 2, a single dose of CCFA-SS at 0.0, 4.4, or 6.6 mg CE/kg was administered when uniform clinical signs of BRD were present in feedlot cattle. Study 3 was conducted in several feedlots to evaluate the efficacy, practicality, and safety of CCFA-SS at 4.4 or 6.6 mg CE/kg compared with a placebo control or tilmicosin for preemptive control of BRD. In Study 1, the effective dose was determined to be 5.35 mg CE/kg; therefore, 4.4 and 6.6 mg CE/kg were selected as the dosages for further field testing. Administration of CCFA-SS at 4.4 or

6.6 mg CE/kg improved treatment success compared with negative controls ($P \leq$" .05 for both doses) in Study 2. In Study 3, a single administration of 4.4 or 6.6 mg CE/kg was comparable to tilmicosin ($P < .001$) and was significantly better than placebo ($P < .001$) for the control of BRD. Using the ear as an administration site was acceptable under field conditions and was well tolerated by all animals. These studies demonstrated that a single administration of CCFA-SS by SC injection in the middle third of the posterior aspect of the ear at 4.4 or 6.6 mg CE/kg is effective, safe, and practical for preemptive control and treatment of the bacterial component of BRD in feedlot cattle. Administration in an inedible tissue results in a short withdrawal time and no injection-site trimming at slaughter.

Introduction

Ceftiofur, a broad-spectrum cephalosporin, can be synthesized in various salt forms. The sodium (Naxcel®/Excenel„â Sterile Powder, Pharmacia Animal Health, Kalamazoo, MI) and hydrochloride (Excenel„â Sterile Suspension, Pharmacia Animal Health) salts of ceftiofur have been approved worldwide (three to five treatments) for treatment of respiratory diseases associated with *Mannheimia* spp *(Pasteurella haemolytica), Pasteurella multocida,* and *Haemophilus somnus* in beef and dairy cattle.[1,2] Both products are also approved for treatment of acute bovine foot rot associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Additional indications are also approved in swine, goats, sheep, horses, day-old chickens, day-old turkey poults, and dogs. The sodium formulation requires reconstitution prior to administration, whereas the hydrochloride formulation is ready to use. Ceftiofur crystalline-free acid sterile suspension (CCFA-SS), the free-acid form of ceftiofur in a sterile oil suspension, is being developed as a single-administration formulation to add to the ceftiofur product family.

Initial dosage-determination and dosage-confirmation studies evaluated a formulation of CCFA-SS containing 100 mg ceftiofur equivalents (CE)/ml administered subcutaneously (SC) in the neck.[3] These studies demonstrated that a single administration of a dose calculated to deliver 4.4 to 5.5 mg CE/kg of body weight was effective for the treatment of naturally occurring bovine respiratory disease (BRD) in feedlot cattle. However, this route of administration was determined to be unacceptable due to the presence of injection-site ceftiofur residues that exceeded established tolerances for extended periods of time.

Alternative routes and sites of administration were considered, and the middle third of the posterior aspect of the ear was subsequently selected as an ideal site for administration of this product. The ear is considered an inedible tissue by the United States Department of Agriculture; and although the ear is a common site for administration of growth promotion implants, it is a novel site for antibiotic administration. A patent has been issued for administration of injectable antibiotics by this route.[4] Administration of drug materials in an inedible tissue results in shorter withdrawal times and precludes the need for injection-site trimming at slaughter.

A formulation containing 200 mg CE/ml was developed to reduce the volume of material injected. A preliminary pharmacokinetic study showed that SC administration of CCFA-SS in the posterior aspect of the ear resulted in more rapid, albeit slightly reduced absorption of ceftiofur than SC administration in the neck. An additional pharmacokinetic study demonstrated that plasma concentrations of ceftiofur and desfuroylceftiofur-related metabolites remained above 0.2 µg/ml for approximately 180 hours after an SC injection of a single dose of CCFA-SS (6.6 mg CE/kg) in t

posterior aspect of the ear. The clinical and field efficacy studies described here were designed and conducted based on this body of information. In all three studies described here CCSF-SS was administered to cattle by SC injection in the middle third of the posterior aspect of the ear.

Materials and Methods

Study 1

The objective of this study was to test the efficacy of several dosages of CCFA-SS for selection of an effective dose that could be administered as a single dose for treatment of BRD. The study was conducted according to the Good Clinical Practices (GCP) guidelines[5] and used a randomized complete-block design. One hundred four Holstein calves weighing 80.4 ± 9.1 kg each were acclimated to slatted-floor calf hutches. Calves were challenged twice with a virulent culture of *M. haemolytica* according to an established model[6] using isolate 86B0721, which was found to have a ceftiofur minimum inhibitory concentration (MIC) of 0.03 µg/ml.[7] The first challenge contained 12 ml with 4×10^7 colony-forming units (CFU)/ml in a weakly acid solution, and the second challenge (administered 4 hours later) comprised 15 ml with 7.7×10^9 CFU/ml without acid. Calves that had an increase of 0.7°C (1.26°F) or more in rectal temperature and a respiratory rate increase of 10 breaths/min or evidence of depression within 48 hours of challenge were ranked by rectal temperature and body weight and randomly assigned to one of seven treatments. Each calf received a single dose of either placebo or CCFA-SS (200 mg CE/ml) at 1.1, 3.3, 4.4, 5.5, 6.6, or 8.8 mg CE/kg.

Calves were clinically evaluated daily for 9 days after treatment, and surviving calves were euthanized at the end of this period for evaluation of lung lesions by estimating the percentage involvement for each lobe (based on consolidation) and by calculating an overall lung lesion score based on previously determined ratios of each lobe to total lung mass.[8] Clinical evaluations and lung lesion scoring were performed by personnel blinded to the treatment group assignments. Lung lesions were evaluated and scored by a board-certified veterinary pathologist. The primary decision variables were cumulative mortality due to BRD through 9 days after treatment, rectal temperature 96 hours after treatment, and lung lesion scores 9 days after treatment.

A linear-linear spline regression was used to model the dose-response curve for each variable. The effective dose for each primary variable was determined as the 90^{th} percentile of the distribution of the knot connecting the two linear phases of the dose-response curve, which was considered to be the beginning of the efficacy plateau. The dosage selected for field testing was to be the highest of the effective dosage predicted by the primary variables that was less than 7.0 mg CE/kg, with the exception that if mortality predicted the highest dosage, mortality would be used regardless of the predicted dosage. Data from one calf were excluded from the statistical analysis due to a dosing error.

Study 2

The objective of this study was to evaluate the efficacy of a single dose of CCFA-SS compared with a placebo for treatment of naturally occurring BRD in feedlot cattle. This 28-day randomized complete-block study was conducted according to GCP guidelines[5] at a feedlot in Idaho. One hundred sixty-two crossbred beef steer calves weighing 229 ± 31.3 kg each were randomly assigned to treatment when they met the following inclusion criteria: rectal temperature 40°C (104°F) or higher, respiratory index = 1 (0 = normal, 1 = abnormal), and depression index greater

than 0 (0 = normal, 1 = mildly depressed, 2 = moderately depressed, 3 = severely depressed). These calves were ranked by rectal temperature and body weight and were randomly assigned to receive a single dose of either placebo or CCFA-SS at 4.4 or 6.6 mg CE/kg. Using standard techniques, a nasal swab was collected from each animal before treatment. Swabs were cultured for the primary BRD bacterial pathogens (i.e., *Mannheimia* spp, *P. multocida, H. somnus*). The MICs for ceftiofur were determined for the BRD pathogens isolated using standard techniques.[7] Respiratory index and depression index were recorded on Days 2, 3, 4, 14, and 28, and cattle were observed on all other study days. Rectal temperature and body weight were recorded on Days 4, 14, and 28. Clinical evaluators remained blinded to the assigned treatments throughout the study. Beginning on Day 4, cattle that still had (or redeveloped) clinical signs of BRD were considered treatment failures and were administered standard feedlot therapy.

Treatment success on Day 14 was the primary decision variable and was defined as an animal that did not receive a second treatment for BRD and was clinically normal on Day 14 (i.e., rectal temperature below 40°C, normal respiration, and mild or no depression). Data were analyzed using one-sided Pearson's chi-square test on the product-binomial table. The hypothesis tested was that the treatment success rate for the CCFA-SS group was less than that for the control group. The study was designed to have approximately 95% power to detect a significant difference if the control success rate was 25% and the treatment success rate was 65%. Power calculations were based on data from a previous study conducted at the same location. Comparisons were made at a = .05. Data from 160 animals were included in the analysis. Data from two animals were excluded due to injury.

Study 3

The objective of this study was to evaluate the efficacy of a single dose of CCFA-SS for preemptive control of BRD in high-risk feedlot cattle, compared with both negative (placebo) and positive (tilmicosin) controls. The practicality and safety of administering the material by SC injection in the posterior aspect of the ear under field conditions were also evaluated. Control was measured by the incidence of BRD in the 28-day period following processing on arrival at the feedlot. This randomized complete-block study was conducted according to GCP guidelines[5] at nine feedlots in six states in the United States (TX, NE, ID, KS, IA, MI). A total of 3911 high-risk, crossbred beef cattle, including bulls, steers, and heifers weighing 236 ± 41.7 kg each were randomly assigned to treatment based on the order through the chute at processing, which occurred within 48 hours after arrival at the feedlot. Cattle received a single dose of vehicle (or sterile saline) or CCFA-SS at 4.4 or 6.6 mg CE/kg by SC injection in the posterior aspect of the ear, or tilmicosin at 10 mg/kg administered SC in the neck. An arrival lot was considered a group of cattle (at least 80 head) that arrived at the feedlot on the same day or were put together within a 6-day period. Following treatment administration, cattle were housed in pens by arrival lots. Pen riders, who remained blinded to the assigned treatment groups throughout the study, observed the cattle daily for 28 days for clinical signs of BRD, signs of ear swelling, or any other problems. Cattle with clinical signs of BRD received a standard feedlot therapy and were considered preemptive treatment failures. On approximately Day 29, cattle were weighed, and ears were palpated to evaluate injection sites.

The primary decision variable was the incidence of BRD through Day 29. The analysis of this variable included only lots in which the BRD morbidity for the controls was at least 20%, suggesting that the animals had been at high risk for BRD. Data were analyzed using weighted analysis of variance (ANOVA) following Freeman-Tukey transformation (one-sided tests). Hypotheses tested included whether CCFA-SS was better than controls and whether it was

comparable to (equal to or better than) tilmicosin. The study was designed to have approximately an 80% power to detect a difference of 12 percentage points in the incidence of BRD, with the incidence assumed to be 36% in the negative controls. Comparisons were made using a = .05. Data from 3878 cattle were included in the analysis after data from 33 animals were excluded from the analysis of efficacy due to incorrect dosing. Data from 32 additional animals were subsequently excluded from results of ear evaluations and average daily gain (ADG) comparisons because final evaluations were missing for these animals.

Results

Study 1

Results of Study 1 are summarized in **TABLE 1.**

TABLE 1. Dosage Determination for Ceftiofur Crystalline-Free Acid Sterile Suspension (CCFA-SS) for Treatment of Experimentally Induced Bovine Respiratory Disease

		CCFA-SS (mg ceftiofur equivalents/kg)					
	Placebo	*1.1*	*3.3*	*4.4*	*5.5*	*6.6*	*8.8*
Number of cattle	11	11	12	12	11	11	12
Cumulative mortality (%)	27.3	9.1*	0.0*	8.3*	9.1*	0.0*	0.0*
Mean rectal temperature 96 hr after treatment (°C)	39.4	39.2	38.7†	38.4†	38.6†	38.6†	38.3†
Mean calculated lung lesion scores (% involvement)	16.7	31.5	16.8	11.2	13.0	9.8	4.9
Lung lesion scores below control group median score (%)	50.0	44.4	33.3	72.7	60.0	90.0‡	100.0‡

Parameter	*Predicted Effective Dosage§ (mg ceftiofur equivalents/kg)*
Mortality	1.80
Rectal temperature 96 hr after treatment	5.35
Lung lesion scores 9 days after treatment	8.51

*Significantly different from placebo ($P = .007$).
†Significantly different from placebo ($P < .001$).
‡Significantly different from placebo ($P \leq .006$).
§90th percentile of the distribution of the knot connecting the two linear phases of the dose–response curve for the variable listed.

The intratracheal challenge model resulted in severe pneumonia, with 27.3% mortality in the placebo control group. The mean mortality rate in the groups treated with CCFA-SS (pooled) (4.3%) was significantly ($P < .01$) lower than the mortality rate in the control group. Mean rectal temperature 96 hours after treatment was 39.4°C (102.9°F) for the control group and ranged from 38.3°C to 39.2°C (101.0°F to 102.6°F) for the groups treated with CCFA-SS. With the exception of calves treated with 1.1 mg CE/kg, all animals treated with CCFA-SS had significantly ($P < .01$) lower temperatures than the control group. Only the 6.6 and 8.8 mg CE/kg groups had median lung lesion scores significantly ($P < .01$) below the median for the control group. Ear carriage was nor for both ears of all animals on all study days. No adverse reactions were reported in this study.

Using dose-selection procedures described above, the effective dose was determined to be 5.35 mg CE/kg, based on rectal temperature 96 hours after treatment. Therefore, 4.4 and 6.6 mg CE/kg were the dosages of CCFA-SS selected for field evaluation.

Study 2

Results of Study 2 are summarized in **TABLE 2**.

TABLE 2. Dosage Confirmation for Ceftiofur Crystalline-Free Acid Sterile Suspension (CCFA-SS) for the Treatment of Naturally Occurring Bovine Respiratory Disease (BRD)

		CCFA-SS (mg ceftiofur equivalents/kg)	
	Placebo	*4.4*	*6.6*
Number of cattle	53	53	54
Treatment successes through Day 14 (%)	54.7	69.8*	70.4*
Treatment successes through Day 28 (%)	64.2	75.5	79.6*
Rectal temperature on Day 4 (°C)	39.8	39.4	39.2*
Cumulative BRD mortality through Day 28 (%)	3.8	0.0	0.0

*Significantly different from negative controls ($P \leq .05$).

Treatment success rates on Day 14 for CCFA-SS at 4.4 and 6.6 mg CE/kg were 69.8% and 70.4%, respectively. Both were significantly more effective than placebo for the treatment of BRD ($P = .05$). On Day 28, the treatment success rate for the 6.6 mg CE/kg treatment (79.6%) was significantly better than for the placebo treatment ($P = .04$); however, the success rate for 4.4 mg CE/kg (75.5%) was not ($P = .10$). Mortality due to BRD was 3.77% for controls, whereas there was no mortality reported for the CCFA-SS treatment groups. *Mannheimia* spp were isolated from 45.1%, *P. multocida* from 26.5%, and *H. somnus* from 6.79% of the nasal swabs collected as cattle entered the study. No adverse reactions were reported. Based on this study, a single dose of CCFA-SS at 4.4 to 6.6 mg CE/kg was confirmed to be an effective treatment for the bacterial component of naturally occurring BRD in feedlot cattle.

Study 3

Results of Study 3 are summarized in **TABLE 3**.

TABLE 3. Efficacy of Ceftiofur Crystalline-Free Acid Sterile Suspension (CCFA-SS) and Tilmicosin in Dosage Confirmation Evaluation of Preemptive Control of Bovine Respiratory Disease (BRD) in Feedlot Cattle

		CCFA-SS (mg ceftiofur equivalents/kg)		*Tilmicosin (mg/kg)*
	Placebo	*4.4*	*6.6*	*10*
Incidence of BRD (%)	39.9	26.6*†	28.2*†	25.1*
Days to first pull (sign of illness)	5.4	6.1†	6.7†‡	5.7
ADG (kg/day)	1.48	1.56†	1.58†‡	1.56‡

*Significantly better than placebo ($P < .001$).
†Equal to or better than tilmicosin ($P < .001$).
‡Significantly better than placebo ($P < .05$).
ADG = Average daily gain.

A total of 3007 cattle were in lots having at least 20% of the controls showed signs of BRD. The incidence of BRD during the 28-day study was 39.9% for the placebo control group, 26.6% for CCFA-SS at 4.4 mg CE/kg, 28.2% for CCFA-SS at 6.6 mg CE/kg, and 25.1% for tilmicosin. Preemptive administration of CCFA-SS or tilmicosin significantly ($P < .001$) reduced the incidence of BRD compared with the placebo control group. In addition, both CCFA-SS doses tested were comparable to results with tilmicosin ($P < .001$). Mortality due to BRD was less than 1% and was not analyzed statistically. The number of days to develop BRD was significantly ($P = .02$) longer in the 6.6 mg CE/kg group than in the placebo control group; however, the 4.4 mg CE/kg and tilmicosin groups were not significantly different from controls. Weight gain through Day 29 was significantly greater in the 6.6 mg CE/kg ($P = .02$) and tilmicosin ($P = .05$) groups than in the placebo group.

Data for the ear administration procedure and tolerance to the procedure are summarized in **TABLE 4**.

TABLE 4. Injection Site Irritation in Feedlot Cattle Treated with Placebo, Ceftiofur Crystalline-Free Acid Sterile Suspension (CCFA-SS), or Tilmicosin

		CCFA-SS (mg ceftiofur equivalents/kg)		*Tilmicosin (mg/kg)*
	Placebo	*4.4*	*6.6*	*10*
No additional restraint required at treatment (%)	98.4	98.2	97.7	99.2
Required reinjection (%)	7.5	5.1	5.6	0.8
Excessive leakage or other problems on day of treatment (%)	1.4	2.8	3.4	0.1
Normal ears or swelling present on or about Day 29 (%)	99.9	97.3	96.1	100
Pus, lesions, or other problems on or about Day 29 (%)	0.1	2.7	3.9	0

Under field conditions, approximately 98% of the cattle receiving an ear injection required no additional restraint beyond that provided by the chute. Reinjection was required in approximately 6% of the cattle injected in the posterior aspect of the ear. Excessive leakage, bleeding, or other problems immediately after injection were observed in approximately 2.54% of the cattle that received ear injections. On approximately Day 29, most of the ears that had been injected with CCFA-SS were normal or had slight to large amounts of swelling, with approximately 2.2% of them considered abnormal. No other local or systemic adverse reactions attributable to CCFA-SS were observed during this study.

Discussion

The efficacy of a single dose of CCFA-SS for the treatment of BRD was initially established in studies that evaluated the product administered SC in the neck.[3] In one of these earlier studies, treatment success rates for CCFA-SS against BRD were 44.4%, 67.1%, and 75.0% for 1.1, 4.4, and 5.5 mg CE/kg, respectively, and 50.6% for tilmicosin. These studies collectively demonstrated that a single SC administration of CCFA-SS at dosages ranging from 4.4 to 5.5 mg CE/kg was effective for the treatment of naturally occurring BRD.

Although CCFA-SS was shown to be an effective treatment for BRD when administered SC in the neck, this route of administration is not acceptable due to the persistence of ceftiofur residues at the injection site for extended periods following administration. Alternate sites and routes of administration were considered, and the middle third of the posterior aspect of the ear was selected as the optimum because the ear is considered an inedible tissue by the United States Department of Agriculture. Using this inedible tissue as the site of treatment administration supports beef quality in two ways: The vast majority of ceftiofur residues are removed from the carcass when the inedible tissue is removed at slaughter and therefore these residues cannot enter the human food chain. Secondly, there is no need for further injection-site trimming from the carcass.

The three studies presented here demonstrate the effectiveness of CCFA-SS administered SC in the middle third of the posterior aspect of the ear for both the control and treatment of naturally occurring BRD in feedlot cattle. The minimum effective dosage for this route of administration is slightly higher (4.4 to 6.6 mg CE/kg) than that shown for SC administration in the neck (4.4 to 5.5 mg CE/kg).[3] This difference is supported by a pharmacokinetic study that confirmed CCFA-SS administration in the posterior aspect of the ear results in more rapid and slightly less complete absorption of ceftiofur from the injection site compared with SC administration in the neck.

Previous studies conducted with CCFA-SS administered in the neck only evaluated the efficacy of CCFA-SS for the treatment of BRD.[3] This work was confirmed and expanded in the present studies, which also demonstrated CCFA-SS efficacy for the control of BRD when administered preemptively to high-risk cattle during processing on arrival at the feedlot. A single dose of CCFA-SS at 4.4 to 6.6 mg CE/kg was found to be comparable to the positive control, tilmicosin, with respect to pull rate (illness rate), time to first sign of illness, and ADG when administered at processing on arrival at the feedlot.

An important component of Study 3 was evaluation of the procedure for injecting CCFA-SS SC in the posterior aspect of the ear. The tolerance of the cattle to this procedure at the time of administration and the tolerance of the ear to the injected material (determined by swelling or other problems) in the month following administration were important findings because the

studies were conducted under field conditions. Overall, the injection procedure was found to be acceptable under these field conditions. For most of the treatment administrators, this was their first experience administering a liquid suspension in the posterior aspect of the ear. Very few cattle required additional restraint, and reinjection was only required in approximately 6% of the animals receiving ear injection. Technique is expected to improve further as injection devices specifically designed for this procedure are developed and experience with the procedure increases. In addition, animal tolerance to the procedure was acceptable, both immediately after injection and during the month following treatment. No animals were removed from the study due to ear problems, and although swelling was still present in ears on Day 29, only approximately 3% to 4% of the ears were considered to be abnormal. The improved ADG of cattle given either dose of CCFA-SS demonstrated that the local reaction to the ear injection had no detrimental effect on the cattle's performance. This is further supported by a separate study that demonstrated that administration of CCFA-SS at 6.6 mg CE/kg concomitantly in the same ear as a growth-promoting implant did not adversely affect feedlot cattle performance.[9]

Conclusion

These studies demonstrated that a single dose of CCFA-SS (200 mg CE/mL) administered SC in the middle third of the posterior aspect of the ear at doses of 4.4 to 6.6 mg CE/kg is effective, safe, and practical for the control and treatment of BRD in feedlot cattle. In addition, since the product is administered in an inedible tissue, there are no injection site trimmings and a short meat withdrawal time applies.

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