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A Comprehensive Review of Ceftiofur Sodium and Hydrochloride Formulations for Treatment of Acute Bovine Foot Rot

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Abstract

Seven well-controlled studies conducted under multiple management conditions demonstrated that ceftiofur, a late-generation veterinary parenteral cephalosporin, is effective for the treatment of bovine foot rot in beef and dairy cattle. Two preliminary dosage titration studies using a challenge model compared the efficacy of ceftiofur (1.1 mg or 2.2 mg ceftiofur equivalents [CE]/kg administered once daily for 3 days) with placebo. One preliminary clinical study evaluated the efficacy of ceftiofur sodium (1.0 mg CE/kg once daily for 3 days) in lactating dairy cows. Two clinical trials evaluated the efficacy of ceftiofur sodium versus placebo for naturally occurring foot rot, and two trials compared the efficacy of ceftiofur sodium or hydrochloride (1.0 mg CE/kg) with oxytetracycline (6.6 or 10 mg/kg), each administered once daily for 3 days, for treatment of acute foot rot in beef cattle. All trials demonstrated the efficacy of ceftiofur for treatment of acute bovine foot rot. Ceftiofur and oxytetracycline were comparable in efficacy, with ceftiofur having excellent injection-site tolerance and short or no milk discard or preslaughter withdrawal.

Introduction

Acute interdigital necrobacillosis, also known as bovine foot rot, interdigital phlegmon, necrotic pododermatitis, foul in the foot, panaritium, or panaris, is an infectious disease and a common cause of lameness in cattle. Any foot can be infected, but most cases occur in the hind legs. The condition is caused by *Fusobacterium necrophorum* subsp *necrophorum,* and *Prophyromonas asaccharolytica* (formerly *Bacteroides melaninogenicus)* also may play a role. Although the pathogenesis of foot rot is not completely understood, bacteria gain entry through abraded skin on

the lower part of the foot. Hard surfaces contribute to foot injury, and continuous wetting likely favors abrasions by softening the interdigital skin.[1] Foot rot is characterized by acute lameness from swelling and necrosis of the interdigital and coronary skin, usually in only one leg. In the acute stage, the exudate of the primary inflammation is often serous and foul smelling.[2] Animals may have a moderate fever (39° to 40°C [103° to 104°F]) and lactating cows experience temporary, but often significant, decreases in milk yield. In the absence of treatment, swelling and necrosis can spread to adjacent tendon sheaths, joint capsules, and bone.[1] Foot rot is rarely fatal, although the occasional animal develops serious joint disease and must be culled from the herd.

The greatest economic impact of bovine foot rot is in dairy operations, where milk production may be affected, and in feedlots, where antimicrobial treatments necessitate withdrawal times that could delay marketing.[1] Although spontaneous recoveries do occur, lameness may persist for several weeks when infections are left untreated, adversely affecting milk production and animal condition, and complications may cause more severe problems that could eventually lead to death or euthanasia of the animal.[1,2] Prompt treatment with parenteral antibiotics and local care of the foot lesion shorten recovery time to 2 to 4 days.[1] A variety of local and systemic antimicrobial treatments have been used, most of which eventually provide a clinical cure; however, individual local treatment requires chemical restraint of the animal for adequate manual restraint of the affected legs and is therefore considered impractical for feedlot cattle or cattle at pasture.[1]

Various antimicrobials, including oxytetracycline, tylosin, sodium sulfadimidine, sulfabromomethazine, sulfamethazine, and procaine penicillin G, have been used to treat interdigital necrobacillosis.[1,3] Oxytetracycline may require large injection volumes and can be associated with injection-site pathology.[4] Oxytetracycline also has a lengthy withdrawal period and in many countries is contraindicated for lactating dairy cows.[5] Because of its prolonged presence in milk, tylosin is contraindicated in lactating dairy cows and has a slaughter withdrawal time of 21 days.[6] Several sulfonamides are approved in the United States for treatment of foot rot, but they are specifically contraindicated for dairy heifers or cows 20 months of age or older and may require prolonged withdrawal times.[7] Penicillin is widely used, but dosages higher than those on the label are often required, milk from treated cows must be discarded a minimum of 48 hours after the last treatment, and the withdrawal time before slaughter is at least 10 days.[8]

Ceftiofur, a broad-spectrum cephalosporin, is active against gram-positive and gram-negative pathogens of veterinary importance, including b-lactamase-producing strains.[9-12] As with other cephalosporins, ceftiofur is bactericidal in vitro, resulting from inhibition of cell wall synthesis. Ceftiofur can be synthesized in different salt forms. The sodium salt of ceftiofur (Naxcel or Excenel Sterile Powder, Pharmacia & Upjohn Animal Health) has been approved worldwide for treatment of respiratory diseases in beef and dairy cattle, swine, and horses. The hydrochloride salt of ceftiofur (Excenel RTU Sterile Suspension) is a ready-to-use formulation approved for treatment of swine and bovine respiratory disease (BRD). Regardless of which ceftiofur salt is administered, dose recovery, drug distribution in tissues, residue concentrations, and metabolites are similar.[10]

Ceftiofur is approved in the United States and Europe for treatment of BRD associated with *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*), *Pasteurella multocida*, and *Haemophilus somnus*.[13,14] In the United States, the dosage for both ceftiofur sodium and ceftiofur hydrochloride is 1.1 to 2.2 mg ceftiofur equivalents (CE)/kg once daily for 3 to 5 days. In Europe

, the dosage for both salts is 1 mg CE/kg BW for 3 days. Investigation of the in vitro activity of ceftiofur sodium against obligatory anaerobic bacteria of veterinary importance, including *F. necrophorum* isolated from bovine liver abscesses and foot rot, revealed ceftiofur was highly active against this organism, with an MIC_{90} of 0.25 µg/ml or less.[12] In a second study, 38 isolates of *F. necrophorum* all had an MIC ranging from 0.016 to 0.062 µg ceftiofur/ml.[15]

Experience with BRD therapy indicated ceftiofur was very safe when administered to cattle, including lactating dairy cows, although ceftiofur should not be given to animals previously found to be hypersensitive to this compound. This experience also afforded the opportunity to monitor for the emergence of resistance in respiratory pathogens. The absence of resistance to ceftiofur by target pathogens (*M. haemolytica, P. multocida,* and *H. somnus*) has been demonstrated in a number of studies since 1988, when the drug was first marketed.[16-18] Preslaughter withdrawal time for ceftiofur is 0 to 8 days and milk discard time is 0 to 2 days, depending on the country.

To establish the efficacy and optimal dose for ceftiofur in the treatment of foot rot, seven well-controlled studies were conducted before approval was obtained for the use of ceftiofur for treatment of bovine foot rot. These seven studies included two dosage titration studies that first evaluated the model's suitability for testing of therapeutic regimens and established the time for treatment after challenge and secondly evaluated two dosage levels for ceftiofur when treatment was initiated immediately after the onset of clinical signs of disease. After determining that 1.0 mg CE/kg was efficacious against foot rot in these preliminary trials, that dosage was subsequently compared with a placebo and a positive control (oxytetracycline) for both induced and naturally occurring foot rot in dairy and beef cattle at multiple locations in the United Kingdom, United States, Canada, and France under a wide variety of management conditions. Ceftiofur hydrochloride was used in one study; all others used ceftiofur sodium.[10] Ceftiofur was given by IM injection in all but one (dosage titration) study, in which the product was given SC. Both routes of injection have been determined to be interchangeable with regard to efficacy and target animal and human safety.[9] A synopsis of these dosage titration and clinical field studies is presented in this paper. These studies provide useful background data to support the use of ceftiofur for the treatment of bovine foot rot.

Dosage Titration Studies

Two dosage titration studies evaluated the efficacy of 1.1 and 2.2 mg CE/kg versus placebo (sterile saline) in an experimentally induced model of acute bovine foot rot (**TABLE 1**).[20] In the first study (Challenge Study 1), 25 yearling cattle were challenged with a mixture of *F. necrophorum* and *P. asaccharolytica* in the interdigital space of three feet to induce bacterial foot rot; the remaining foot was not infected and served as a control. Cattle were randomly allocated to treatment with ceftiofur sodium (1.1 or 2.2 mg/kg) or 5 ml sterile water. All treatments were given by IM injection once daily for 3 days beginning 3 days after challenge. Lesions were evaluated 3 days after challenge and 3, 7, and 14 days after initiation of treatment by observers who were unaware of the treatment groups. Lesions were scored on a scale of 0 to 5 (0 = no lesion; 5 = severe lesion). Lameness was evaluated on Days 1, 2, 3, 7, and 14 and scored for each animal on a 0 (no lameness) to 3 (severe lameness) scale (**TABLE 2**). No statistically significant differences were detected among the three groups, although greater clinical improvement was observed in the two ceftiofur groups than in the placebo group. By the time treatment was initiated 3 days after challenge, some animals had advanced stages of foot rot that were refractory to treatment. In the subsequent

dosage titration and clinical field studies, treatment was initiated when animals first exhibited clinical signs of lameness, which is consistent with the current recommendation for treatment of foot rot.[1]

TABLE 1. Summary of Dosage Titration and Clinical Field Studies of Ceftiofur for Treatment of Acute Bovine Foot Rot

Location/ Study	*Study Conditions*	*Animals*	*Treatment Regimens*
Dosage Titration and Efficacy Studies with Bovine Foot Rot Challenge Models			
US/ Challenge Study 1	Treatment started 3 days after challenge.	25 Yearling cattle (8 or 9/treatment)	Ceftiofur sodium 1.1 mg CE/kg IM Ceftiofur sodium 2.2 mg CE/kg IM 5 ml sterile water IM
US/ Challenge Study 2	Treatment started when clinical signs appeared.	39 Yearling cattle (13/treatment)	Ceftiofur sodium 1.1 mg CE/kg IM Ceftiofur sodium 2.2 mg CE/kg IM Sterile water (placebo) IM
US/ Challenge Study 3	Lesion and lameness scores translated into cure/no cure.	41 Crossbred beef cattle (13 or 14/treatment)	Ceftiofur hydrochloride 1 mg CE/kg SC Oxytetracycline 10 mg/kg SC Sterile water (placebo) SC
Field Trials with Naturally Occurring Bovine Foot Rot			
France/ Field Trial 1	Responses judged 1 = very efficacious, 2 = efficacious, 3 = ineffective 1 day after last treatment; examined for signs of relapse 9 days after treatment began	27 Lactating dairy cows	Ceftiofur sodium 1.0 mg CE/kg IM
UK/ Field Trial 2	Treatment success = no lameness 4 days after treatment	42 Lactating Holstein-Friesian cows	Ceftiofur sodium 1.0 mg CE/kg IM
11 Sites in North America/ Field Trial 3	Clinical cure = reduction in lameness score, no to moderate swelling, and healed or healing lesions, with no relapse	88 Beef and dairy cattle (43 or 45/treatment)	Ceftiofur sodium 1.1 mg CE/kg IM Sterile water (placebo)
Canada/ Field Trial 4	Clinical evaluation of lameness	307 Yearling beef steers (128 or 129/treatment)	Ceftiofur sodium 0.1 mg CE/kg IM Ceftiofur sodium 1.0 mg CE/kg IM Oxytetracycline 6.6 mg/kg IM

CE = ceftiofur equivalents.

TABLE 2. Lameness Scoring Criteria for Evaluations of Treatments for Bovine Foot Rot in Dosage Titration and Clinical Field Studies

Lameness Score	*Interpretation*
0	Normal
1	Slight lameness; puts some weight on foot but moves readily
2	Moderate lameness; reluctant to put weight on foot, moves slowly
3	Severe lameness; holds foot up at intervals, reluctant to move or place entire weight on foot, prefers to lie down

In Challenge Study 2 (**TABLE 1**), a challenge model similar to that in the first study (other than treatment was initiated as soon as lameness was evident) was used to evaluate ceftiofur sodium (1.1 and 2.2 mg/kg IM) versus placebo in 39 yearling cattle. Lesions and lameness (**TABLE 2**) were evaluated 2 days after challenge and 3, 7, and 10 days after treatment. Lesions were scored the same as the previous challenge study. Lesion and lameness scores were added together to provide a total score for data analysis.

Challenged animals began to exhibit lameness 2 days after challenge, and treatment was initiated at that time. Both ceftiofur regimens were significantly ($P < .0001$) superior to placebo in reducing the severity of lesions and lameness. *F. necrophorum* was isolated from 100% of the lesions cultured from 12 animals in the placebo group on Day 3 but in only 38% of the lesions from ceftiofur-treated cattle. On Day 7, *F. necrophorum* was isolated from all nine placebo-treated animals but only from one of four ceftiofur-treated animals cultured at that time. Following 3 days of treatment with ceftiofur, *F. necrophorum* was eliminated in the majority of treated cattle by Day 10. Changes in scores for lameness, lesions, and for these evaluations combined were averaged for each animal for each day (**TABLE 3**). Differences among treatments were evaluated using the general linear model (GLM) procedure of SAS (SAS Institute). Results were not significantly different between 1.1 and 2.2 mg/kg; however, both ceftiofur treatments were significantly ($P < .0001$) better than placebo in reducing the severity of foot lesions and lameness scores. The lower dosage rate (1.1 mg/kg) was used in subsequent field trials.

TABLE 3. Combined Lesion* and Lameness† Scores for Yearling Cattle (n = 39) with Induced Foot Rot Treated with Ceftiofur Sodium or Placebo Daily for 3 Days in a US Dosage Titration Study (Challenge Study 2)

Day	*CeftiofurSodium (1.1 mg CE/kg)*	*Ceftiofur Sodium (2.2 mg CE/kg)*	*Placebo*
0	7.77	8.00	5.85
3	4.38	5.54	13.69
7	1.08	1.08	6.69
10	0.69	0.92	5.77

*Lesions scored 0 (none) to 5 (severe).
†Lameness scored 0 (none) to 3 (severe).
CE = ceftiofur equivalents.

Field Trials

An open-label field trial evaluated the efficacy of ceftiofur sodium in the treatment of acute bovine foot rot (present no more than 3 days) in 27 lactating dairy cows in France[15] (**TABLE 1**; Field Trial 1). Animals were excluded if they had been treated with any other antibiotic within 15 days before the study began. Participating veterinarians examined each cow, confirmed the diagnosis of foot rot, and recorded the degree of lameness (**TABLE 2**), the amount of edema, and the extent of necrotic lesions. Cows were then treated with ceftiofur at 1.0 mg/kg by IM injection once daily for 3 consecutive days. No placebo was used in this study. Response to therapy, evaluated 1 day after the last treatment, was rated as very efficacious, efficacious, or ineffective by the participating veterinarians based on lameness, edema, and lesion scores assessed before initiation of treatme and 1 day after the last treatment. Treated animals were also observed daily for 9 days by the

owner for evidence of relapse after the treatment was initiated. One day after treatment, ceftiofur treatment was rated very efficacious for 48%, efficacious for 33.5%, and ineffective for 18.5% of the treated cattle. No relapses were reported. This small, uncontrolled, and unblinded study supported earlier challenge model findings that ceftiofur sodium administered IM at 1.0 mg/kg once daily for 3 consecutive days was an effective treatment for acute bovine foot rot

A multilocation field efficacy study was conducted in the United Kingdom (**TABLE 1**; Field Trial 2), and 42 lactating Holstein-Friesian cows with naturally occurring bovine foot rot were treated with ceftiofur sodium at 1.0 mg/kg by IM injection once daily for 3 consecutive days.[15] No additional local or general treatments (e.g., paring, bandaging) were permitted, and no untreated or positive control groups were included in this unblinded study. Cows were evaluated by the study veterinarian 1 and 4 days after the end of treatment. Treatment success was defined as no lameness 4 days after the end of treatment, and failure was defined as no improvement by 1 day after the end of treatment or persistent lameness 4 days after the end of treatment. Thirty-one of the 42 cows (74%) were completely cured 4 days after the final (third) treatment. Eight of the 11 animals that were not cured had appreciable improvement in the lesion score despite some residual lameness.

Controlled Efficacy Studies

A well-controlled, multilocation, blinded, randomized study of 88 (47 beef cattle and 41 dairy cows) cattle was conducted at 11 sites in North America (**TABLE 1**; Field Trial 3).[21] Samples from naturally occurring lesions of bovine foot rot were taken for anaerobic culture from 33 animals to confirm the presumed diagnosis of foot rot at the test sites before treatment began. Microbiologic examination provided 28 *P. asaccharolytica* and 21 *F. necrophorum* isolates from the 33 animals sampled, and both organisms were frequently (61%) present in many of the lesions. These results confirmed the presence of foot rot in enrolled animals. A front foot was affected for 55% of the feedlot cattle and 20% of the dairy cattle. Cattle at each site were randomly assigned to receive either ceftiofur sodium at 1.1 mg CE/kg or sterile water (control) administered by IM injection once daily for 3 consecutive days. No concurrent antibiotics, antiseptics, paring of necrotic tissue, or topical antiseptics or dressings were used, and animals were not treated for foot rot within 30 days prior to enrollment. Cattle were observed at enrollment and 1 and 3 days after treatment. Clinical cure was defined as a minimum two-point reduction in lameness scores (**TABLE 2**), moderate to no swelling, healed or healing lesions on the affected foot, and no observable relapse at a final examination between Days 12 and 15.

The effectiveness of treatment with ceftiofur was tested by calculating the percentage cured ([number cured/number treated] x 100), and transforming this percentage using the Freeman-Tukey double arcsine transformation.[22] The difference between transformed cure rates was tested using the one-sided GLM procedure of SAS. Factors considered in the analysis were type of operation (dairy or beef), location within type, treatment, type x treatment interaction, and error. Treatment was found to be the only significant factor in the analysis. Differences were declared significant when $P \leq .05$. The cure rate for ceftiofur was 69.6% for beef cattle and 54.6% for dairy cattle (**TABLE 4**). This difference was not significant ($P = .33$). Under a variety of management conditions for beef and dairy operations, the combined cure rate was 62.2% for the ceftiofur treatment versus 14% for the placebo group ($P < .003$).

TABLE 4. Clinical Cure Rates for Ceftiofur Sodium or Placebo Administered Daily for 3 Days Against Naturally Occurring Foot Rot in Beef and Dairy Cattle Evaluated in Field Study at 11 North American Sites (Field Trial 3)

	*% (Number Cured/Number Treated)**	
	Ceftiofur Sodium (1.1 mg CE/kg IM)	*Placebo (Sterile Water)*
Beef cattle (six feedlots)	69.6 (16/23)	16.7 (4/24)
Dairy cows (five dairies)	54.6 (12/22)	10.5 (2/19)
Totals (11 sites)	62.2† (28/45)	14.0 (6/43)

*Cure was defined as a minimum two-point reduction in lameness score, moderate to no swelling, healed or healing lesions, and no relapse.
†Significantly different from placebo ($P < .003$).
CE = ceftiofur equivalents.

Two clinical trials evaluated the efficacy of ceftiofur versus oxytetracycline, one in a challenge model (Challenge Study 3) and one in a field study (Field Trial 4). In the challenge study, 41 crossbred beef cattle were challenged with an inoculum of *F. necrophorum* and *P. asaccharolytica* in the interdigital space of three feet; the remaining foot served as a within-animal control.[23] When acute foot rot developed, animals were individually evaluated and randomly assigned to one of three treatments: ceftiofur hydrochloride sterile suspension 1.0 mg CE/kg (n = 14), oxytetracycline hydrochloride 10 mg/kg (n = 14), or sterile water (n = 13). All treatments were administered by SC injection once daily for 3 days. The dosages of ceftiofur and oxytetracycline conformed to those registered for treatment of BRD in the European Union. Animals were evaluated daily for lameness (**TABLE 2**) and lesions were individually scored (0 to 5) on Days 3, 7, and 10 after the first treatment. Lesion and lameness scores were translated into a cure/no cure result for analysis. Cure rates were compared using the Pearson chi-square statistic.

In the challenge study, ceftiofur was significantly better than placebo in reducing lesion scores on both Days 7 ($P = .008$) and 10 ($P = .036$), whereas oxytetracycline was significantly ($P = .047$) better than placebo only on Day 10 (**TABLE 5**). On all 3 days of evaluation, lesion scores were similar for ceftiofur and oxytetracycline using the bootstrap technique. Comparison by the Pearson chi-square statistic indicated that ceftiofur was significantly better than placebo in reducing lameness on Day 7 ($P = .004$), whereas oxytetracycline was not ($P = .071$). By Day 10, 67% of animals treated with ceftiofur exhibited no lameness, compared with 46% for both oxytetracycline and placebo. Neither ceftiofur nor oxytetracycline had significantly better lameness cure rates than placebo on Day 10. Additionally, lameness cure rates were not significantly different between ceftiofur and oxytetracycline. This study confirmed that treatment with ceftiofur was significantly better than placebo in reducing lesion scores and lameness associated with bovine foot rot. Results with ceftiofur treatment were similar to those for oxytetracycline.

TABLE 5. Lesion and Lameness Cure Rates in a US Trial for Ceftiofur Hydrochloride versus Oxytetracycline or Placebo Given Daily for 3 Days Against Induced Foot Rot in Beef Cattle (Challenge Study 3)

	Ceftiofur Hydrochloride (1.0 mg CE/kg SC)	*Oxytetracycline (10 mg/kg SC)*	*Placebo (5 ml SC)*
No. of animals enrolled	14	14	13
Lesion cure rate (%)			
Day 3	24	12	13
Day 7	50*	38	23
Day 10	60*	60*	39
Lameness cure rates (%)			
Day 7	42*	15	0
Day 10	67	46	46

*Significantly different from placebo ($P < .05$).
CE = ceftiofur equivalents.

The larger, randomized controlled trial was conducted to compare two dosages of ceftiofur sodium with oxytetracycline for treatment of acute foot rot in 307 crossbred yearling steers in a Canadian feedlot (**TABLE 1**; Field Trial 4).[4] The diagnosis of acute interdigital necrosis was based on the presence of characteristic clinical signs. Animals were excluded if they had been previously treated for interdigital necrosis, had received an antibiotic within the previous 30 days, had more than one affected foot, or had other systemic or local diseases. Animals were blocked by order of enrollment and randomly assigned to receive ceftiofur at either 0.1 mg or 1.0 mg/kg or oxytetracycline at 6.6 mg/kg. All treatments were administered by IM injection once daily for 3 days. The lower dosage of ceftiofur was included to define a nonzero, ineffective dose. Cattle were observed daily during the treatment period and 1 day after the last treatment for signs of lameness. Response to treatment was monitored by a veterinarian who was not aware of group assignments. Animals that developed concurrent diseases were removed from the trial and treated for the condition according to the feedlot's standard procedures. A preplanned interim analysis was conducted after the first 150 cattle were enrolled. Interim analysis revealed that the success rate for 50 cattle treated with ceftiofur at 0.1 mg CE/kg was significantly ($P < .001$) lower than for cattle in the other groups. This group, therefore, was discontinued for animal welfare reasons, and results for these 50 animals were disregarded in all evaluations and analyses.

Results for ceftiofur at 1.0 mg/kg and oxytetracycline were not significantly different at the interim evaluation. Final cure rates (absence of lameness on Day 4) are presented in **TABLE 6**). None of the 76 cattle that were considered treatment failures in the final analysis (35 from the ceftiofur group and 41 from the oxytetracycline group) became chronically ill, and all responded to additional antibiotic treatment. It was concluded that ceftiofur at 1.0 mg/kg and oxytetracycline at 6.6 mg/kg given for the same duration were equally effective against naturally occurring foot rot in feedlot cattle. The shorter withdrawal time for ceftiofur was considered by investigators to be a great advantage over oxytetracycline as a treatment of bovine foot rot in animals nearing market weight.[4]

TABLE 6. Clinical Cure Rates 4 Days after Initiating Treatment with Ceftiofur Sodium or Oxytetracycline Once Daily for 3 Days for Naturally Occurring Foot Rot in Cattle in a Canadian Feedlot (Field Trial 4)

Treatment	*% Cure Rates* (Number Cured/Number Treated)*
Ceftiofur (0.1 mg CE/kg IM)	10 (5/50)†
Ceftiofur (1.0 mg CE/kg IM)	73 (94/129)ns
Oxytetracycline (6.6 mg/kg IM)	68 (87/128)ns

*Cure rate based on absence of lameness in animals that were lame before treatment was initiated.
†Findings at interim analysis conducted after 50 animals were enrolled in each group. This group was discontinued after that evaluation because of obvious lack of efficacy.
nsResults for ceftiofur (1.0 mg CE/kg) and oxytetracycline were not significantly different.
CE = ceftiofur equivalents.

Discussion

In vitro studies first established the sensitivity of *F. necrophorum*, the main pathogen associated with bovine foot rot, to ceftiofur. Additional information on the sensitivity of *P. asaccharolytica* to ceftiofur might have been useful, but the pathogen is not a common or available diagnostic isolate. Because ceftiofur had demonstrated in vitro activity against members of the genus *Bacteroides*,[12] there was reason to believe it would prove effective against *P. asaccharolytica* as well.

None of these studies measured levels of ceftiofur-related metabolites at the site of infection. Such information could help explain the clinical success demonstrated in these trials. However, both the dose titration and North American studies provided evidence that treatment with ceftiofur sodium is superior to a negative control. Additionally, ceftiofur treatment eliminated *F. necrophorum* from the site of infection in the majority of animals in the second dosage titration study, an indicator that therapeutic ceftiofur concentrations reached the infection site. As a practical matter, a validated analytical methodology was not available for interdigital tissue.

Only the North American study sampled foot rot lesions for the microbiological isolation of the causative agents. It is, however, accepted that acute foot rot can be readily diagnosed based on the characteristic site, lesion, and odor.[1,2] Therefore, additional microbiological testing would have added only limited information but considerable effort and expense for sampling, transporting, and culturing under strict anaerobic conditions. Moreover, evidence from the second dosage titration study had already demonstrated that treatment eliminated the causative agent in most animals.[20]

The ceftiofur dosages selected for the dose titration studies were based on regimens approved for the treatment of BRD. Although not specifically selected for the treatment of bovine foot rot, these ceftiofur regimens had demonstrated safety for the target animal and milk and meat discard times had been established.[19,20] All of the clinical studies described here clearly support the efficacy of a minimum dosage of 1.0 mg CE/kg for the treatment of bovine foot rot. Advanced disease that was refractory to treatment in the first dosage titration study confirmed recommendations to start treatment as soon as clinical signs of lameness appear.[1,2] In experimentally induced disease, delaying treatments for several days after the onset of clinical signs led to the development of severe lesions and prolonged recovery times.[1,2]

Although the efficacy trials conducted in the United Kingdom, United States, Canada, and France followed different study designs and protocols, all studies demonstrated the efficacy of ceftiofur for the treatment of acute bovine foot rot in the absence of any additional local or general treatment. It is recognized that the scoring systems and definitions of success differed somewhat for the various studies. Although lesion scores were used only as ancillary parameters in the UK study (treatment success was based on absence of lameness), profound reductions in lameness and lesion scores were used to evaluate treatment success in the multilocation North American study. The French study used an overall evaluation by the practicing veterinarian as the definition of cure. Scores were recorded as ancillary parameters only. The UK study, which was not blinded, provided evidence of the efficacy of ceftiofur sodium in the treatment of acute bovine foot rot because evaluation of success was based on an objective, binary, and easy-to-measure parameter (absence of lameness). The North American study used parameters that were more difficult to evaluate objectively (swelling, lameness, lesion scores); however, the scoring systems used were satisfactory for statistical comparisons, and the trial provided useful and meaningful data.

The relative differences in cure rates observed among the field efficacy studies may be based on the different parameters chosen for evaluation and also on the different housing and management systems utilized in various countries. Housing conditions for cattle vary from typical North American feedlot conditions for beef cattle to dairy farms, where cows are kept either entirely indoors on slatted floors or partly outdoors for grazing. Differing management conditions in the field trials most likely contributed to varying degrees of severity of the condition, which was treated at different intervals after clinical signs appeared and resulted in varying cure rates. Ceftiofur was effective in reducing clinical signs of foot rot in all the studies, regardless of the different housing and management conditions and of the varying protocols.

In the North American study, treatment with ceftiofur sodium was tested against a negative control group, which had a spontaneous cure rate of 14%. The UK study was designed to enroll as many animals as possible by testing the treatment efficacy against this rate. This nontraditional approach permitted efficacy testing without a positive or negative control group. In the absence of a control group, the relative benefit of treatment was evaluated by comparison with this spontaneous cure rate.

Foot rot is a common disease seen frequently in clinical cattle practice. There are few well-controlled clinical studies and no placebo-controlled studies reported in the literature. This review presents the clinician with evidence-based medicine in a variety of management and geographic conditions to support rational treatment decisions.

Although these clinical trials focused primarily on efficacy, the safety of ceftiofur was amply demonstrated by the fact that no adverse effects of treatment were observed in nearly 300 animals treated at 1.0 to 2.2 mg CE/kg. This result is consistent with the excellent safety record of ceftiofur since its introduction in 1988. Furthermore, no or short milk discard and preslaughter withdrawal are necessary when ceftiofur, either as the hydrochloride or sodium salt, is used according to label indications, dosage, and route of administration. In animals nearing market weight, the lack of preslaughter withdrawal is an advantage.

Conclusion

Ceftiofur in its sodium or hydrochloride salt is now approved as a safe and efficacious treatment acute bovine foot rot associated with *F. necrophorum* and *P. asaccharolytica* by regulatory agencies around the world. Approved dosages range from 1.0 to 2.2 mg CE/kg once daily for 3 to 5

consecutive days. The efficacy of ceftiofur is documented in well-controlled and multilocation trials under laboratory challenge and natural disease conditions. This review presents the clinician with evidence-based medicine in a variety of management and geographic conditions to support rational treatment decisions.

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