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Evaluation of ceftiofur crystalline free acid sterile suspension for control of metritis in high-risk lactating dairy cows

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ABSTRACT

Two studies were conducted to determine if clinical metritis could be prevented or decreased in at-risk lactating dairy cows by a single treatment with Excede Sterile Suspension (ceftiofur crystalline free acid sterile suspension [CCFA-SS]) administered within 24 hours after an abnormal calving. Study 1 was a preliminary study and study 2 was a clinical trial (designed to confirm the results of study 1). In both studies, abnormal calving was defined as cows that had dystocia (required assistance), twins, abortion, retained fetal membranes for 12 hours or more, or any combination thereof. A randomized block design with cows blocked on order-of-entry within dairy without regard to parity was used in both studies. In study 1, cows that had abnormal calving from six commercial dairies were randomly assigned to either untreated control (N = 122) or 6.6 mg ceftiofur equivalents/kg of body weight sc in the base of the ear (CCFA-SS, N = 121), within 24 hours after calving. Cows with normal calving during the enrollment period received no treatment and were included for observational purposes (N = 122). Health observations and rectal temperatures were recorded daily, and physical examinations were conducted on Days 1 ± 1, 7 ± 2, 14 ± 2, and 21 ± 2, and uterine swabs (for bacterial culture) were collected from a subsample of cows on Days 3 or 4, 7 ± 2, 14 ± 2, and 21 ± 2. These observations were made by treatment-blinded personnel. In study 2, cows with abnormal calving from 12 commercial dairies were assigned to receive either saline (control, N = 247) or CCFA-SS (N = 247) within 24 hours after calving. Health observations and rectal temperatures were recorded daily, and physical examinations were conducted on Days 0 to 2, 7 ± 1, and 14. In study 1, the incidence of metritis on Day 14 ± 2 was 20.2% versus 36.8% for CCFA-SS and control, respectively, with an odds ratio of 2.30 ($P < 0.05$). In study 2, incidences of metritis on Day 14 were 28.7% versus 43.5% for CCFA-SS and saline, respectively, with an odds ratio of 1.92 ($P < 0.05$). Rectal temperatures on Days 1 and 2 and the average for the first 6 days were lower ($P < 0.05$) for CCFA-SS compared with control cows for both studies. Treatment of cows with a single dose of CCFA-SS within 24 hours after abnormal calving reduced the incidence of subsequent metritis in lactating dairy cows.

1. Introduction

Metritis in dairy cows is associated with substantial economic loss because of reduced milk production and reproductive performance and increased risk of culling

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[1–3]. A cow with puerperal metritis has an abnormally enlarged uterus and a fetid watery red-brown uterine discharge within 21 days (most commonly 10 days) after partrition. Systemic signs of illness (e.g., decreased milk yield, dullness, or other signs of toxemia) and fever 39.5 °C or higher, within 21 days after parturition might also be present [4]. The reported incidence of metritis ranges widely from 10% to 36% in dairy cows [1,5–8]; the lactational incidence rate was 21% in a large survey including 97,316 cows with 181,322 lactations [9]. Benzaquen et al. [10] reported that cows that had abnormal calving, defined as dystocia, twins, RFM, abortion, or any combination thereof, were at higher risk of developing metritis than cows that had normal calving. The adjusted odds ratio for development of metritis for cows with an abnormal calving was 4.8 compared with cows that had normal calving, and the incidence of metritis was 41% for cows with abnormal calving compared with an incidence of 21% for cows with normal calving [10].

Although incidences of individual predisposing factors are relatively low, a high percentage of dairy cows have one or more predisposing factors for metritis. For example, the incidence of dystocia is reported to be between 5.8% and 13.7% [6,7,11,12] and as high as 36.6% [13]. The odds ratio that cows with dystocia will develop metritis ranged from 1.2 to 4.0 [6–8,11,12]. Further, the percentage of cows that deliver twins varied from 1.4 to 8.9 and the odds ratio for developing metritis after twins ranged from 2.0 to 5.4 [6–8,12,14].

Retained fetal membranes were reported to affect between 1.3% and 11.8% of dairy cows and the odds ratio for developing metritis in cows with a RFM ranged from 6.0 to 11.9 [5,7,11,12]. The percentage of cows with an abortion ranged from 4.1% to 6.0% [6,13,15] and the odds ratio for cows that had an abortion developing metritis ranged from 1.5 to 7.9 [6,8,11,12]. Other risk factors for metritis included ketosis, mastitis, primiparity, milk fever, and displaced abomasum [8,11].

Uterine bacterial load is high in most cows after parturition and *E. coli* and *Arcanobacterium pyogenes* (current name *T. pyogenes*) are the most prevalent bacteria isolated from the uterine lumen. *Fusobacterium necrophorum*, *Prevotella spp.*, and *Bacteriodes spp.* have also been specifically associated with presence of, or development of, metritis [16–18]. It is believed that *E. coli* paves the way for invasion of other bacteria, and the combination with *T. pyogenes*, *F. necrophorum*, and *Prevotella spp.* act synergistically to increase the severity of disease [16,19].

Currently, recommended metritis treatments include primarily the use of systemic antibiotics, particularly cephalosporins, uterine antimicrobial boluses, or both [20,21]. Although these treatments can reduce the duration of metritis, it was hypothesized that treatment of dairy cows at high risk of developing metritis with Excede Sterile Suspension (ceftiofur crystalline free acid sterile suspension [CCFA-SS]) soon after calving would reduce the number of cows that subsequently developed metritis. Thus, two studies were designed with the objective of evaluating whether treatment of dairy cows that had abnormal calving (i.e., dystocia, twins, abortion, RFM, or any combination thereof) with CCFA-SS within 24 hours after calving would decrease the percentage of cows that subsequently developed metritis. A preliminary study (study 1) was conducted in six farms to test the validity of the concept and results were used to refine the design of a clinical trial (study 2) that was conducted at 12 farms. Post study 2, selected data were collected from nine of the 12 farms to evaluate potential longer term effects of treatment.

2. Materials and methods

These studies were approved by the Pfizer Institutional Animal Care and Use Committee and conducted in accordance with EC Directive 86/609/EEC for animal experiments.

2.1. Preliminary study (study 1)

2.1.1. Treatments and experimental design

Study 1 was conducted according to a multidairy randomized design with cows blocked by order-of-entry within dairy without regard to parity. The objective was to demonstrate the principle of controlling metritis in at-risk cows and was designed to detect significance using the one-sided test at the $P = 0.05$ level. Target enrollment of 20 cows per treatment at each of six sites was based on 80% power to detect a 15 to 20 percentage unit difference in incidence of metritis with the assumption of 40% metritis in the control group. Cows at high risk of developing metritis were assigned to one of two treatments: control that received no treatment ($N = 122$) or CCFA-SS that received a single administration of 6.6 mg/kg of body weight (BW) of ceftiofur crystalline free acid sterile suspension (Excede, 200 mg/mL, Pfizer Animal Health, Madison, NJ, USA; http://pfizerah.com) sc at the base of the ear ($N = 121$). The dose of CCFA-SS was based on a BW that was estimated using a breed-specific heart girth measuring tape (Nasco Inc., Atkinson, WI, USA). A third group was included for observational purposes (NTX; $N = 122$) and included cows that had normal calving (no identified risk factor for developing metritis) during the period that control and CCFA-SS cows were enrolled and received no treatment. Each day that a block was initiated by assignment of a cow with abnormal caving to treatment, the next available cow that calved normally on that day was selected as the NTX for that block. All personnel (except the treatment administrator) who were involved in the study were blinded to treatment. Furthermore, the treatment administrator performed no other study-related activities.

2.1.2. Cows and enrollment

Lactating dairy cows ($N = 365$) from six commercial dairies (at least 60 cows per dairy) in the United States were enrolled within 24 hours after calving from August through November of 2007 (summer and fall). To be included in the control or CCFA-SS treatment, cows must have experienced an abnormal calving event, defined as dystocia, RFM, twins, abortion, or any combination thereof. Dystocia was defined as a delayed or difficult parturition and each dairy used a four-point scoring system with specific interpretation by the dairy in which 0 = no dystocia or intervention, 1 = slight assistance, 2 = considerable force needed, and