EFFICACY OF SUSTAINED RELEASE NEEDLE-LESS CEFTIOFUR SODIUM IMPLANTS IN TREATING CALVES WITH BOVINE RESPIRATORY DISEASE

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SUMMARY

Three experiments were conducted to determine preliminary efficacy of sustained release needle-less implants in effecting a cure in calves with bovine respiratory disease. One hundred and twenty beef calves with a rectal temperature $\geq 40^\circ\text{C}$ and shallow or labored respiration and coughing were used in these experiments. Four groups (1-ceftiofur sodium injections [days 1, 2, and 3], 2-ceftiofur sodium needle-less implants [days 1, 2, and 3], 3-ceftiofur sodium needle-less implants [days 1 and 3], and 4-ceftiofur sodium needle-less implants [day 1] were included. All treatments contained 250 mg of ceftiofur sodium and were administered intramuscularly in the neck after diagnosis of bovine respiratory disease. Experiment 1 included 20 calves (group 1-10 calves and group 3-10 calves; 213 to 255 kg) and calves were monitored for clinical efficacy. Experiment 2 included five calves per group (all four groups; 164 to 192 kg) and calves were bled frequently after treatment for desfuroylceftiofur (the primary ceftiofur metabolite) concentrations. Experiment 3 included 20 calves per group (all four groups; 160 to 205 kg) and calves were monitored for clinical efficacy. Blood desfuroylceftiofur concentrations remained above the minimum inhibitory concentration for Pasturella haemolytica, Pasturella multocida, and Haemophilus somnus for 24 hours after injection and 72 hours after implantation ($P < .05$). Mortalities and the number of calves with a positive response and relapse response were similar ($P > .25$) among the four groups. In summary, the administration of one-250 mg ceftiofur sodium needle-less sustained release implant was as efficacious in treating bovine respiratory disease as three daily 250 mg injections of ceftiofur sodium.

INTRODUCTION

Bovine respiratory disease (BRD) is the most economically important infectious disease of calves in North American feedlots (Jensen et al., 1976; Thomson, 1980; Church and Radostits, 1981; Wohlgemuth and Herrick, 1986; Baker et al., 1986). BRD not only threatens the medical health of cattle but also the financial health of the producers who raise them. Morbidity rates as high as 69% and mortality rates as high as 15% have been reported (Kelly and Janzen, 1986). The high incidence of this disease necessitates that feedlot veterinarians and cattlemen must continually rely on the use of antimicrobial agents to deal with BRD. Conventional drug therapy 1) evokes stress on the animal provoking the precarious condition of the animal, 2) requires time and effort, and 3) may require daily applications over a period of three or more days. Because of the time and effort requirements, cattle with minimal symptoms may not be treated promptly intensifying the risk on performance and mortality. Since there is no method to completely protect cattle against BRD, feedlot veterinarians and cattlemen need a convenient delivery system for an antimicrobial that will reduce or eliminate the stress and the time and effort in delivering the antimicrobial to infected animals. These experiments utilized ceftiofur sodium in a delivery system that facilitates therapy and sustains the delivery of the antimicrobial over days. The objective was to determine preliminary efficacy of needle-less ceftiofur sodium implants at a reduced treatment interval and a reduced total dosage in treating calves with BRD.
METHODS AND MATERIALS

Mixed breed beef steer calves that had been shipped through one or more yards were purchased for these experiments. Upon arrival in Canyon, TX, calves were administered ear tags, a pour-on insecticide (Tiguvon®), an anthelmintic (Synanthic®), an anabolic implant (Synovex®S), and vaccines against bovine respiratory syncytial (modified live), parainfluenza3 (modified live), infectious bovine rhinotracheitis virus (modified live), and bovine virus diarrhea (killed) viruses (Horizon® 1+Vac 3) and clostridium chauvoei, septicum, novyi, sordellii, perfringens types C and D, and haemophilus somnus (Vision® 7 Somnus with Spur®), placed in outdoor pens, and observed for signs of BRD. If a calf was suspected of having BRD, 1) it was given an illness score (Table 1, 2) rectal temperature was collected, and 3) body weight was collected. Based on this data, the diagnosis of BRD was confirmed or rejected (Table 1). One hundred and twenty calves were diagnosed with BRD and treated as follows.

Treatment Groups. Experiment 1 included groups 1 and 3 and Experiments 2 and 3 included all four treatment groups.

1. Ceftiofur injections (three doses-days 1, 2, and 3)
2. Ceftiofur implants (three doses-days 1, 2, and 3)
3. Ceftiofur implants (two doses-days 1 and 3)
4. Ceftiofur implants (one dose-day 1)

Experiments 1, 2, and 3 included 10, 5, and 20 calves per group, respectively. Calves assigned to the injection group (group 1) were administered 250 mg of ceftiofur sodium (Naxce® l) at each injection. Calves assigned to the needle-less implant groups (2, 3, and 4) were administered 250 mg of ceftiofur sodium in biodegradable implants. The total quantity of ceftiofur sodium for groups 1, 2, 3, and 4 were 750 mg, 750 mg, 500 mg, and 250 mg, respectively, and differed among groups because of frequency of administration. All treatments were administered intramuscularly in the neck. The day of initial treatment was designated as day 1.

Delivery System and Needle-less Implants. The remote delivery system used operates on the basis of compressed air (DeNicola et al., 1996a). The needle-less implants were delivered at 26,152 cm/second (858 feet/second) producing 3.07 X 10^5 g-cm (22.15 foot-pounds) of kinetic energy (Kesler and Favero, 1989; Jacobson et al., 1995; Willis et al., 1994; DeNicola et al., 1996a). This was accomplished with a fixed regulator attached to the delivery device set at approximately 1100 pounds per square inch (psi). A tank containing compressed air was attached to the regulator. The needle-less implants are capable of being delivered remotely (Kesler and Favero, 1989; Willis et al., 1994; DeNicola et al., 1996a; DeNicola et al., 1996b; DeNicola et al., 1997a; DeNicola et al., 1997b; Jacobsen et al., 1995; Kesler and Favero, 1997; Kesler, 1997; Kesler et al., 1998) and were manufactured from two major components. The outer shell was manufactured from food grade biodegradable and biocompatible food additives (Kesler et al., 1998) and was 0.635 cm in diameter and 2.0 cm long. The second component was the ceftiofur sodium (along with some tableting lubricant and controlled release excipients) and was 0.40 cm in diameter and 1.4 cm long (Kesler, 1993).
It has been demonstrated that upon contact with the skin, the needle-less implant first causes the skin to stretch (Kesler et al., 1998). After stretching, the implant penetrates the skin by producing a slit in the skin. After penetration has occurred, the skin then contracts back to its original form leaving behind a small slit through the skin. The entry slit is shorter than the diameter of the projectile (Swartz et al., 1997). Minimal bleeding occurs after penetration and is followed by scab formation (Kesler and Favero, 1989). The implant does not carry a portion of the animal's hide into the wound. It only leaves a small raised welt on the skin at the point of implant entry (Kesler and Favero, 1989). Upon entry into living tissue the outer shell dissolves within six hours (Kesler, 1997). Kesler et al. (1998) and Swartz et al. (1997) have demonstrated that cortisol concentrations were not significantly increased by administration of the needle-less implants. Further, necropsy of treated animals have revealed that other than damage caused by implant penetration early after administration, the tissue at the administration site was normal (DeNicola et al., 1996a; Swartz et al., 1997).

Experiment 1
These 20 calves with a positive diagnosis of BRD were 213 to 255 kg (238.3 ± 2.6 kg). Since the recommended dose of ceftiofur sodium is 1.1 to 2.2 mg per kg these calves received 1.05 mg per kg ceftiofur sodium (4.6% less than recommended). Calves were administered ceftiofur sodium immediately after positive diagnosis and were processed through the chute for all treatments. Rectal temperature and body weight of the calves were collected on days 1, 2, 3, 4, 5, 6, and 14. Calves were observed daily (for 21 days) for the collection of data described in Table 1. The data were collected by an investigator unaware of which treatments were administered to the calves.

Experiment 2
These 20 calves with a positive diagnosis of BRD were fitted with a jugular catheter and bled. They were then treated and bled 1, 3, 5, 7, 9, 12, 16, and 24 hours after the first treatment. Calves were also bled on the same schedule after the second (groups 1, 2, and 3) and third (groups 1 and 2) treatments. All calves were bled 36, 48, 60, and 72 hours after the first treatment. Blood plasma was harvested from the blood samples within six hours after collection by centrifugation at 2,000 x g. Plasma was stored at -20°C until assayed for desfuroylceftiofur metabolites.

Desfuroylceftiofur concentrations (the major plasma ceftiofur metabolite; Jaglan et al., 1992) were determined from the blood plasma by the procedure described by Jaglan et al., (1989 and 1990). The procedure determines desfuroylceftiofur metabolites in plasma. The method involves first reducing the metabolites bound to macromolecules (Jaglan et al., 1990). Because desfuroylceftiofur is easily oxidized, it was derivatized with iodoacetamide to stabilize the sulfhydryl group of the molecule. After cleanup using solid-phase extraction techniques, the derivatives were determined via HPLC.

On day one the calves were 164 to 192 kg (177.9 ± 1.8 kg) and received on the average 1.4 mg of ceftiofur sodium per kg of body weight at each treatment which is within the recommended per treatment dose (1.1 to 2.2 mg per kg).

Experiment 3
After diagnosis of BRD 80 calves were randomly assigned to one of the four treatment groups. Calves were 160 to 205 kg (182.7 ± 1.2) and received on the average 1.4 mg of ceftiofur sodium per kg of body weight at each treatment. Calves were administered ceftiofur sodium immediately after positive diagnosis and were processed through the chute for all treatments. Rectal temperature and
body weight of the calves were collected on days 1, 4, 6, 14, and 21. Calves were observed daily (for 21 days) for the collection of data described in Table 1. The data were collected by an investigator unaware of which treatments were administered to the calves.

Experiments 1 and 3
Calves were classified with a positive response or a negative response on the sixth day (Table 1). All negative response calves were then removed from their pen and administered florfenicol (Nuflor®; 3.6 g) on days 6 and 9. If a calf with a positive response appeared abnormal after day 6 and met the same criteria as defined for a positive diagnosis (Table 1), it was diagnosed as a relapse response. Calves with a relapse response were removed from their pens and administered florfenicol (Nuflor®; 3.6 g) at that time and three days later. All mortalities within 30 days after the initial treatment were recorded and calves that died were necropsied for the cause of death.

Analysis. The positive response, relapse response, and mortalities (Experiment 1 and 3) were analyzed by chi-square analysis (Cochran and Cox, 1957). Rectal temperature, illness score, anorexia score, respiratory rate, and nasal discharge score (Experiment 1) were analyzed by split-plot analysis of variance (Gill and Hafs, 1971) as 2 x 2 x 6 factorial designs with response (positive or negative/relapse response), treatment (groups 1 and 3), and time (days 1, 2, 3, 4, 5, and 6) as the main effects. Rectal temperature, illness score, anorexia score, respiratory rate, and nasal discharge score (Experiment 3) were analyzed by split-plot analysis of variance (Gill and Hafs, 1971) as 2 x 4 x 3 factorial designs with response (positive or negative/relapse response), treatment (groups 1, 2, 3, and 4), and time (days 1, 4, and 6) as the main effects. Areas under the blood desfuroylceftiofur response curve were determined mathematically and were analyzed by analysis of variance (Cochran and Cox, 1957). The blood desfuroylceftiofur concentrations were also used to determine the time that blood desfuroylceftiofur concentrations remained above the minimum inhibitory concentration (Robb, 1994).

RESULTS

Although 24 hour post-treatment blood desfuroylceftiofur profiles in calves treated with ceftiofur sodium via injections or needle-less implants were not identical (Fig. 1), area under the curve was not affected (P > .10) by method of administration or frequency of administration. The mean peak amplitude of desfuroylceftiofur was greater (P < .05) and the mean interval from treatment to peak was less (P < .05) in calves administered ceftiofur sodium via injection than implantation. Blood desfuroylceftiofur concentrations remained above the minimum inhibitory concentrations for Pasteurella haemolytica, Pasteurella multocida, and Haemophilus somnis for 24 hours after injection and 72 hours after implantation (P < .05).

In Experiment 1 the positive response rate, relapse rate, and mortality rate for groups 1 and 3 were similar (P > .25; Table 2). No clinical data were collected from calves in Experiment 2. In Experiment 3, the positive response rate, relapse rate, and mortality rate were similar (P > .25; Table 3) for all four groups. In Experiments 1 and 3 combined, 94% of the calves were classified with a positive response. Although, 55 of the calves (59% of the positive response calves) in Experiments 1 and 3 met the same criteria as defined for a positive diagnosis greater than six days after the initial treatment, this is within the range previously reported for commercial ceftiofur (Smith et al., 1993;
Smith et al., 1994a; Smith et al, 1994b) and expected for calves used in this study and administered Naxcel® for BRD (Bechtol, unpublished data).

Five of the calves (6%) in Experiment 3 died 15 to 28 days (21.6 ± 2.6 days) after initiation of the experiment as a result of complications associated with BRD. All calves that died were considered to have responded to treatment by day six; however, they were classified as a relapse response after day six. The mortality rate was within the range previously reported (Smith et al., 1993; Smith et al., 1994a; Smith et al., 1994b) and for cattle used in this study and administered Naxcel® for BRD (Bechtol, unpublished data).

As reported in Tables 2 and 3, mean rectal temperature decreased (P < .01) after treatment in both Experiments 1 and 3. In Experiment 1, no other effects or interactions were significant (P > .25) and mean rectal temperature decreased similarly. In Experiment 3, the response (P < .01) and treatment (P < .05) effects and the treatment by response interaction (P < .05) were significant. Mean rectal temperature for positive and negative/relapse response calves in groups 1 and 4 were similar; however, they were greater for negative/relapse response calves in groups 2 and 3 than for positive response calves (Experiment 3). Mean rectal temperature for the calves administered more than one ceftiofur sodium treatment decreased more rapidly than for calves administered only one ceftiofur sodium treatment (Experiment 3). After the third injection, mean rectal temperature increased to day 6 which was not apparent in the calves that received ceftiofur implants.

Mean body weight remained constant (P > .25) over the first six days in Experiments 1 and 3 regardless of response (P > .25) or treatment (P > .25) and then increased for the positive response calves. In Experiment 3, all positive response calves gained an average of 23.9 kg (1.2 kg/day) during the 20 days after initial treatment. The changes in mean illness scores, anorexia scores, respiratory rates, and nasal discharge scores were similar to the changes in mean rectal temperature.

DISCUSSION

BRD, also referred to as pneumonia and shipping fever (Fulton, 1987), has a multifactorial etiology involving a complex interaction between stressors and viruses that act separately or together to suppress the defense mechanisms in the lung and predisposes the animal to bacterial pneumonia (Roth, 1987; Confer et al., 1988). Potential causes of immunosuppression, such as environmental, physical, or psychological stress, lead to greater susceptibility to BRD. BRD in cattle is most frequently associated with Pasteurella haemolytica (Confer, 1988); however, Pasteurella multocida and Haemophilus somnus are also isolated in BRD cases (Frank, 1983). Pasteurella haemolytica and Pasteurella multocida are usually sensitive to sulfonamides, penicillin G, ampicillin, amoxicillin, tetracyclines, spectinomycin, tilmicosin, and ceftiofur sodium (Lofgreen, 1988; Hjerpe, 1993; Morock et al., 1993; Baker, 1993; Hansen et al., 1993).

Ceftiofur sodium is approved by the FDA for treatment of BRD (The Upjohn Co., 1988; The Upjohn Co., 1991; Veterinary Medicine Publishing Group, 1997). Similar to our study, other studies have reported a high positive response rate to ceftiofur sodium injections (Smith et al., 1993; Smith et al., 1994a; Smith et al., 1994b). FDA approval of ceftiofur sodium is for daily application three consecutive days. Additional therapy may be given on days 4 and 5 for animals which do not show a satisfactory response after the initial three treatments (Veterinary Medicine Publishing Group,
Our high relapse response rate, although disappointing, was within the response rate in the literature (Smith et al., 1993; Smith et al., 1994a; Smith et al., 1994b) and typical for cattle purchased from this vendor (Bechtol, unpublished data).

All calves (regardless of method of administration) exceeded the minimum inhibitory concentration for Pasteurella haemolytica, Pasteurella multocida, and Haemophilus somnus by one hour after treatment. The time that blood desfuroylceftiofur concentrations remained above the minimum inhibitory concentration was only 24 hours for the calves administered ceftiofur sodium by injection compared to 72 hours for the calves administered ceftiofur sodium by implantation. This may be why one needle-less implant was as effective in treating BRD as three daily injections although the total dose was lower with the administration of one implant. Reduced stress associated with the delivery of one implant may also facilitate response to treatment as Christie et al. (1977) have demonstrated that glucocorticoids compromise antimicrobial recovery to BRD. One chute handling is less stressful than three daily chute handlings.

All treatment groups had a high relapse response. This may suggest that the duration of time that blood ceftiofur sodium concentrations needed to be elevated above the minimum inhibitory concentration for Pasteurella haemolytica, Pasteurella multocida, and Haemophilus somnus is greater than 72 hours in this situation. Relapse response might have been decreased if ceftiofur sodium injections had been administered for five days or if a second needle-less implant of ceftiofur sodium had been administered on day 4 (72 hours after the first treatment). In addition, it may be prudent to consider other antimicrobials for use in this system.

The needle-less delivery system is convenient for use and evokes minimal or no stress in treated animals (Kesler et al., 1998). Kesler and Favoro (1997) reported one of three responses in treated cattle: no response, a kick, or a curious look by the treated animal. Some advantages of needle-less implant delivery as compared to syringe and needle delivery as described by Kesler et al. (1998) follow.

1. Labor and time savings reducing the cost associated with drug therapy.
2. Reduced stress to animals removing the detrimental effects of stress on performance and recovery to drug therapy.
3. Reduction in tissue damage (bruising) or animal injury and/or death in the absence of chute processing.
4. Elimination of needles removes the possibility of broken needles in animals and the need for their disposal.
5. Reduced risk of mis-dosing since there is no diluting and mixing involved.
6. The system ensures no animal-to-animal contact with needles and blood products, therefore the potential spread of disease is significantly reduced.

In summary, it is concluded that the administration of one 250 mg ceftiofur sodium needle-less sustained release implant was as efficacious in treating BRD as three daily injections of 750 mg of ceftiofur sodium. Remote delivery of one needle-less implant would be a convenient, non-stressful method of providing therapy to calves with bovine respiratory disease. As done in this study, administration of the needle-less implants in the neck would have no effect on high quality cuts of meat (Dexter et al., 1994; George et al., 1995a; George et al., 1995b; George et al., 1996).
LITERATURE CITED


The Upjohn Co. 1991: The first-choice solution for shipping fever. The Upjohn Co., Kalamazoo, MI.


Veterinary Medicine Publishing Group. 1997: Veterinary Pharmaceuticals and Biologicals. Veterinary Medicine Publishing Co., Lenexa, KS.


Table 1. Definitions used to classify bovine respiratory disease (BRD) and monitor recovery after treatment

Positive Diagnosis of BRD:

1. Rectal Temperature $\geq 40^\circ$C
2. Respiratory Index = 1
   0 = normal
   1 = shallow or labored with moderate to excessive coughing
3. Depression Index $\geq$ 1
   0 = normal-bright, alert and responsive
   1 = mild-head down but responsive to stimulation
   2 = moderate-head down, still evident after stimulation
   3 = severe-reluctant to rise, head down, dull eyes

Illness Recovery Indicators Monitored:

1. Rectal Temperature
2. Illness Score-the sum of the respiratory and depression indexes
3. Anorexia
   0 = Normal-full feed.
   1 = Mild anorexia (eating but not filled).
   2 = Severe anorexia (not eating).
4. Respiratory Rate
   0 = $< 45$ breaths/minute
   1 = $\geq 45$ breaths/minute but $\leq 75$ breaths/minute
   2 = $\geq 75$ breaths/minute
5. Nasal Discharge
   0 = none
   1 = excessive, serous
   2 = copious, mucopurulent

Negative Response to Treatment and Relapses with BRD:

1. Negative Response-calves with the following criteria 6 days post-treatment.
   a. Rectal temperature $\geq 40^\circ$C
   b. Illness score $\geq$ illness score on day 1 and administered alternative medication.
2. Relapses-positive response calves with the following criteria > 6 days post-treatment.
   a. Rectal temperature $\geq 40^\circ$C
   b. Illness score $\geq$ illness score on day 1 and administered alternative medication.

Table 2. Response of calves with bovine respiratory disease (BRD) administered ceftiofur sodium via conventional injection or needle-less implants
<table>
<thead>
<tr>
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<th>Treatment Group&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>3</th>
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<td>Positive Response&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(n)</td>
<td>9/10</td>
<td>9/10</td>
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<td></td>
<td>(%)</td>
<td>90%</td>
<td>90%</td>
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<tr>
<td>Relapses&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(n)</td>
<td>5/9</td>
<td>4/9</td>
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<td></td>
<td>(%)</td>
<td>56%</td>
<td>44%</td>
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<tr>
<td>Mortalities&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0/10</td>
<td>0/10</td>
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<td></td>
<td>(%)</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>day 1</td>
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<td>41.0 ± .2</td>
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<td>day 6</td>
<td>39.8 ± .1</td>
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<td>day 14</td>
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<td>Illness Score:</td>
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<td>day 1</td>
<td>3.3 ± .2</td>
<td>3.2 ± .1</td>
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<td>day 6</td>
<td>1.6 ± .3</td>
<td>1.3 ± .3</td>
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<td>day 14</td>
<td>1.2 ± .4</td>
<td>.9 ± .4</td>
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<td>Body Weight (kg):</td>
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<td>day 1</td>
<td>238.4 ± 3.0</td>
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<td>day 6</td>
<td>240.8 ± 3.7</td>
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<td>day 14</td>
<td>246.2 ± 2.0</td>
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<sup>a</sup>Treatments were as follows.
1-ceftiofur sodium injections (three doses-days 1, 2, and 3).
3-ceftiofur sodium needle-less implants (two doses-days 1 and 3).

<sup>b</sup>See text for definitions.
Table 3. Response of calves with bovine respiratory disease (BRD) to ceftiofur sodium treatment administered via conventional injection or needle-less implants

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<th>3</th>
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<td>(%)</td>
<td>100%</td>
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<td>Temperature (°C):</td>
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<td>day 1</td>
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<td>3.3± .1</td>
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</tr>
<tr>
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<td>1.2± .2</td>
<td>1.6± .2</td>
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<td>Body Weight (kg):</td>
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<td></td>
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<tr>
<td>day 1</td>
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<td>182.2±2.5</td>
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<td>186.2±2.9</td>
<td>186.3±3.1</td>
<td>180.8±3.1</td>
<td>184.8±2.5</td>
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<sup>a</sup>Treatments were as follows.
1-ceftiofur sodium injections (three doses-days 1, 2, and 3).
2-ceftiofur sodium needle-less implants (three doses-days 1, 2, and 3).
3-ceftiofur sodium needle-less implants (two doses-days 1 and 3).
4-ceftiofur sodium needle-less implants (one dose-day 1).

<sup>b</sup>See text for definitions.

<sup>c</sup>Mortalities occurred 15 to 28 days (21.6 ± 2.6 days) after the initial treatment.
Figure 1. Mean desfuroylceftiofur concentrations in calves treated with ceftiofur sodium via injections (diamonds) or needle-less implants (squares; Experiment 2).