Control of Bovine Respiratory Disease, With and Without Co-Morbidity by Otitis Media, In Dairy Heifers Comparing Gamithromycin, Tulathromycin, or No Medication at a Commercial Development Facility*

Richard D. Linhart DVM, DACT and Gordon W. Brumbaugh DVM, Ph.D, ACVIM, ACVCP, ELS

Objective
To compare the control of bovine respiratory disease (BRD) in dairy heifers using Zactran® (gamithromycin), Draxxin® (tulathromycin) or no metaphylaxis in recently weaned dairy heifers.

Results
• In the 42-day observation period, heifers in the gamithromycin group had less bovine respiratory disease than heifers in the tulathromycin group
• Heifers treated with gamithromycin had a lower risk of otitis media as compared to tulathromycin treated heifers
• For every 15 heifers treated with gamithromycin, 1 less heifer required treatment because of BRD, than those that received tulathramycin

Conclusion
• ZACTRAN and DRAXXIN reduced treatment rates and improved ADG compared to controls
• In this study, ZACTRAN was superior to DRAXXIN in reducing the first treatment rate

Introduction
Optimal dairy heifer development begins at conception and must be maintained all the way through introduction into the milking herd. Respiratory disease affects up to 11.2% of weaned dairy heifers making it the most common condition affecting them, and 97.9% require antimicrobial treatment. The risk of BRD is multifactorial and requires management practices that reduce the risk of neonatal disease.

The developing dairy heifer lives with the risk of developing BRD anytime throughout her life, but the risk becomes greater when the heifer is moved from individual housing to group housing because of commingling and other stressors. The appropriate use of antimicrobials may be effectively utilized at times of increased risk of BRD.
Trial Design

1,567 heifers from 11 different dairies were enrolled in a study to assess the efficacy of Zactran® (gamithromycin) versus Draxxin® (tulathromycin) versus no metaphylaxis (negative control). ZACTRAN was administered to 631 heifers, DRAXXIN was administered to 621 heifers, and 315 heifers served as negative controls. The label dose of each antimicrobial was administered at the time of weaning (removal from the calf hutch) with a 2-day post metaphylactic interval (PMI). Animals were commingled in pens of 12 animals per pen at weaning, observed for signs of BRD for 42 days, and treated according to the study protocol if diagnosed with BRD following the PMI. Any heifer that died during the 42-day observation period was necropsied to determine the cause of death.

Results

34.55% to 47.94% of calves that were enrolled in this study were subsequently treated for BRD. This study showed that the use of antimicrobial medication to control BRD, with or without otitis media, in weaned dairy heifers provided improved health and ADG benefits. ZACTRAN was superior to DRAXXIN for control of BRD, and BRD with co-morbidity by otitis media (Table 1 and Figure 1). Both antimicrobials were superior to no medication (no metaphylaxis), requiring fewer treatments for BRD and/or otitis media. Mortality was not different among the treatment groups. Average daily gain was superior in calves receiving metaphylaxis as compared to those that did not receive a metaphylactic antibiotic.

During the 42-day duration of this study, for every 7 heifers that received ZACTRAN, there was one less heifer that required treatment because of BRD than for the control group (Number Needed to Treat). For every 15 heifers medicated with DRAXXIN, there was one less heifer that required treatment because of BRD for the control group. For every 15 heifers that received ZACTRAN, there was one less heifer that required treatment because of BRD than for those that received DRAXXIN.

Table 1 Outcome variables: means (SEM) by group and P-values for the overall effect of experimental treatment (i.e., testing the null hypothesis that no difference was present among groups) during the 42-d study

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Tulathromycin</th>
<th>Gamithromycin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRD Morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRD 1 Treatment1,%</td>
<td>47.94a (2.82)</td>
<td>41.38a (1.98)</td>
<td>34.55b (1.89)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BRD 2 Treatments,%</td>
<td>6.98 (1.44)</td>
<td>6.12 (0.96)</td>
<td>4.91 (0.86)</td>
<td>0.4</td>
</tr>
<tr>
<td>BRD 3 Treatments,%</td>
<td>0.00 (0.00)</td>
<td>0.48 (0.28)</td>
<td>0.64 (0.32)</td>
<td>0.94</td>
</tr>
<tr>
<td>BRD 4 Treatments,%</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.16 (0.16)</td>
<td>0.99</td>
</tr>
<tr>
<td>BRD Treatment Success2,%</td>
<td>84.11 (2.99)</td>
<td>84.82 (2.24)</td>
<td>84.86 (2.43)</td>
<td>0.98</td>
</tr>
<tr>
<td>BRD Case Fatality3,%</td>
<td>1.33 (0.93)</td>
<td>1.12 (0.67)</td>
<td>1.84 (0.91)</td>
<td>0.83</td>
</tr>
<tr>
<td>BRD Mortality,%</td>
<td>0.63 (0.45)</td>
<td>0.48 (0.28)</td>
<td>0.79 (0.35)</td>
<td>0.79</td>
</tr>
<tr>
<td>Overall Mortality,%</td>
<td>0.95 (0.55)</td>
<td>0.48 (0.28)</td>
<td>0.95 (0.39)</td>
<td>0.59</td>
</tr>
<tr>
<td>Treated: otitis media4,%</td>
<td>16.19 (2.08)</td>
<td>12.40 (1.32)</td>
<td>12.84 (1.33)</td>
<td>0.25</td>
</tr>
<tr>
<td>Treated: BRD &amp;/or otitis media5,%</td>
<td>61.59a (2.74)</td>
<td>51.05b (2.01)</td>
<td>45.96b (1.98)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ADG,lbs</td>
<td>1.71a (0.04)</td>
<td>1.85b (0.03)</td>
<td>1.83b (0.03)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

1Values with different superscripts within a row are significantly different (P ≤ 0.05).
2Bovine respiratory disease (BRD) with or without otitis media (BRD only + BRD and otitis). Percent of heifers that received 1st treatment was calculated using the number originally enrolled in the respective treatment group.
3Treated only once because of BRD (with or without otitis media) during the study, and did not die.
4Treated at least once because of BRD (with or without otitis media) and died due to respiratory disease.
5BRD and otitis + otitis only.
6BRD morbidity + otitis only.
Conclusions

In this study, antimicrobial metaphylaxis with Zactran® (gamithromycin) and Draxxin® (tulathromycin) improved calf health and ADG. ZACTRAN was superior to DRAXXIN, improving the first treatment rate by 15.5% (34.55% vs. 41.38%). ZACTRAN and DRAXXIN reduced overall treatment rates and improved ADG vs. controls. ZACTRAN and DRAXXIN delivered comparable results in all other trial metrics.

ZACTRAN IMPORTANT SAFETY INFORMATION: For use in cattle only. Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older, or in calves to be processed for veal. The effects of ZACTRAN on bovine reproductive performance, pregnancy and lactation have not been determined. Subcutaneous injection may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter. NOT FOR USE IN HUMANS. KEEP OUT OF REACH OF CHILDREN.

150 mg/mL ANTIMICROBIAL

For subcutaneous injection in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.

DESCRIPTION

ZACTRAN® Injection for Cattle is a ready to use sterile parenteral solution containing gamithromycin, a macroclide sub-class, 7a-azalide antimicrobial. Each mL of ZACTRAN contains 150 mg of gamithromycin as the free base, 1 mg of monothioglycerol and 40 mg of succinic acid in a glycerol formal vehicle.

The chemical name of gamithromycin is 1-Oxa-7-azacyclotetradecan-15-one,13(12)-6-deidoe-3-c-methyl-3-O-methyl-alpha-l-hexaoxypranoyl

Residue Warning: Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

The effects of ZACTRAN on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection of ZACTRAN may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter.

ADVERSE REACTIONS

Transient animal discomfort and mild to moderate injection site swelling may be seen in cattle treated with ZACTRAN.

CLINICAL PHARMACOLOGY

The macroclide antimicrobials as a class are weak bases and as such concentrate in some cells (such as pulmonary leukocytes). Prolonged exposure of extracellular pulmonary pathogens to macrolides appears to reflect the slow release of drug from its intracellular reservoir to the site of action, the pulmonary epithelial lining fluid (ELF). It is the ELF that is relevant to the successful treatment and control of BRD. Gamithromycin is primarily bacteriostatic at therapeutic concentrations. However, in vitro bactericidal activity has been observed at concentrations of 10 µg/mL (Mueller–Hinton broth) and after exposure to the 6-hour and 24-hour plasma samples derived from cattle dosed at 6 mg gamithromycin/kg BW. Macrolides typically exhibit substantially higher concentrations in the alveolar macrophages and ELF as compared to concentrations observed in plasma. Gamithromycin concentrations in the ELF and ELF cells exceed the concentrations observed in the plasma. Postmortem gamithromycin concentrations in ELF exceed the MIC₅₀ of M. haemolytica, H. somni and P. multocida through at least 72 hours after drug administration. Because M. haemolytica, P. multocida and H. somni are extracellular pathogens, drug concentrations in the ELF are considered to be clinically relevant. The postmortem area under the concentration-time curve (AUC) observed in lysed ELF cells (e.g., alveolar macrophages) are at least 300-times greater than that in the plasma. Although published studies suggest that inflammation can increase the release of drug from macropathogens and neutrophils, these high concentrations in the alveolar macrophages should not be considered indicative of the magnitude or duration of response to the pathogens for which this product is indicated.

ZACTRAN administered subcutaneously in the neck of cattle at a single dosage of 6 mg/kg BW is rapidly and completely absorbed, with peak concentrations generally occurring within 1 hour after administration. Based upon plasma and lung homogenate data, the terminal half-life (T½) of gamithromycin is approximately 3 days. In vitro plasma protein binding studies show that 20% of the gamithromycin binds to plasma protein, resulting in free drug available for rapid and extensive distribution into body tissues. The free drug is rapidly cleared from the systemic circulation with a clearance rate of 712 mL/hr/kg and a volume of distribution of 25 L/kg. Dose proportionality was established based on AUC over a range of 1 mg/kg BW to 9 mg/kg BW. Biliary excretion of the unchanged drug is the major route of elimination.

The minimum inhibitory concentrations (MICs) of gamithromycin were determined for BRD isolates obtained from calves enrolled in BRD treatment field studies in the U.S. in 2004 using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). Isolates were obtained from pre-treatment nasopharyngeal swabs from each enrolled calf and from calves removed from the study due to BRD. The results are shown below in Table 1.

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Years of isolation</th>
<th>No. of isolates</th>
<th>MIC₅₀ (µg/mL)</th>
<th>MIC₉₀ (µg/mL)</th>
<th>ME range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. haemolytica</td>
<td>2004</td>
<td>89</td>
<td>0.5</td>
<td>1</td>
<td>0.25 to 3</td>
</tr>
<tr>
<td>P. multocida</td>
<td>2004</td>
<td>29</td>
<td>0.5</td>
<td>1</td>
<td>0.12 to 3</td>
</tr>
<tr>
<td>H. somni</td>
<td>2004</td>
<td>32</td>
<td>0.5</td>
<td>0.5</td>
<td>0.25 to 1</td>
</tr>
</tbody>
</table>

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

The effectiveness of ZACTRAN for the treatment of BRD associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni was demonstrated in a field study conducted at four geographic locations in the United States. A total of 497 cattle exhibiting clinical signs of BRD were enrolled in the study. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10. The percentage of successes in cattle treated with ZACTRAN (58%) was statistically significantly higher (p<0.05) than the percentage of successes in the cattle treated with saline (19%). The effectiveness of ZACTRAN for the treatment of BRD associated with M. haemolytica was demonstrated independently at two U.S. study sites. A total of 502 cattle exhibiting clinical signs of BRD were enrolled in the studies. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. At each site, the percentage of successes in cattle treated with ZACTRAN on Day 10 was statistically significantly higher than the percentage of successes in the cattle treated with saline (74.4% vs. 24% (p<0.001), and 67.4% vs. 46.2% (p=0.002)). In addition, in the group of calves treated with gamithromycin that were confirmed positive for M. haemolytica (pre-treatment nasopharyngeal swabs), there were more calves at each site (45 of 57 calves, and 5 of 6 calves) classified as successes than as failures. The effectiveness of ZACTRAN for the control of respiratory disease in cattle at high risk of developing BRD associated with Mannheimia haemolytica and Pasteurella multocida was demonstrated in two independent studies conducted in the United States. A total of 467 crossbred beef cattle at high risk of developing BRD were enrolled in the study. ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within one day after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10 post-treatment. In each of the two studies, the percentage of successes in the cattle treated with ZACTRAN (86% and 78%) was statistically significantly higher (p=0.0019) and (p=0.0016) than the percentage of successes in the cattle treated with saline (36% and 59%).

ANIMAL SAFETY

In a target animal safety study in healthy, six-month old beef cattle, ZACTRAN was administered by subcutaneous injection at 6, 18, and 30 mg/kg body weight (1, 3, and 5 times the labeled dose) on Day 0, 5, and 10 (3 times the labeled administration frequency). Injection site discomfort (neck twisting, attempts to scratch or lick the injection site, and pawing at the ground) was observed in calves in the 18 mg/kg BW and 30 mg/kg BW groups at 10 minutes post-treatment following each injection. Mild to moderate injection site swelling and pathology changes consistent with inflammation were observed in the gamithromycin-treated groups. Other than injection site reactions, no clinically relevant treatment-related effects were observed.

STORAGE CONDITIONS

Store at or below 77°F (25°C) with excursions between 59-86°F (15-30°C). Use within 18 months of first puncture.

HOW SUPPLIED

ZACTRAN is available in three ready-to-use bottle sizes. The 100, 250 and 500 mL bottles contain sufficient solution that will treat 10, 25 and 50 head of 550 lb (250 kg) cattle respectively.