

Field Efficacy Study of Gamithromycin for the Control of Bovine Respiratory Disease in Cattle at High Risk of Developing the Disease

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ABSTRACT

Bovine respiratory disease (BRD) is one of the most economically significant sources of losses arising from poor performance and mortalities in cattle entering feedlots. Antibacterial treatments are administered to cattle in the feedlots therapeutically or prophylactically for control of pathogens associated with BRD. Gamithromycin is an azalide 15-membered semi-synthetic macrolide antibiotic that has been developed for the treatment and control of BRD. Two separate field studies were conducted at

feedlots in Texas and Nebraska to evaluate the efficacy of a single treatment with gamithromycin administered subcutaneously at 6.0 mg/kg body weight for control of BRD in calves at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, the primary pathogens responsible for outbreaks of BRD. The proportion of treatment successes in the group treated with gamithromycin was significantly higher ($P < 0.05$) at both sites than in the saline-treated control group. There were no deaths associated with BRD in either group at either site. A single treatment with gamithromycin at the time of entry at the feedlot provided rapid and pro-

Table 1. Summary of animal descriptions by location

Study	Location	Number of animals enrolled	Number of animals treated	Number of animals in analysis	Breed	Approximate age (mo)	Weight range (kg)
1	Texas	159 (68 M, 91 MC)	159	154	Cross	6-8	170-256
2	Nebraska	308 F	308	308	Cross	6-10	130-293

F=female; M=male, MC=male castrate

longed therapeutic and preventive efficacy against the primary pathogens responsible for outbreaks of clinical BRD for at least 10 days after treatment in each study.

INTRODUCTION

Bovine respiratory disease (BRD) is one of the most economically significant sources of losses arising from poor performance and mortalities in cattle entering feedlots. Financial losses due to death, reduced feed efficiency, and treatment costs are estimated to run between \$500 million and \$900 million annually.¹⁻³ Weaning, trucking, processing, commingling, changing weather, and overcrowding are stressful, thus compromising the immune system, leaving the animals susceptible to invasion by different infectious agents.⁴⁻⁸ The most common infectious viruses affecting cattle entering the feedlot include bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), bovine respiratory syncytial virus (BRSV), and parainfluenza type-3 virus (PI-3).^{4,5,8} Pathology caused by these viruses creates the opportunity for bacteria, such as *Mannheimia haemolytica* and *Pasteurella multocida*, to invade the lungs. In a study of feedlots in 12 states in 1999, the USDA-APHIS reported a 14% incidence of clinical BRD.² Prevention, control, and treatment of BRD, relies primarily on vaccines and antibiotics, but other alternatives, including genetic selection and various management practices, also have been evaluated in recent years.^{4,8-10}

Gamithromycin is an azalide 15-membered semi-synthetic macrolide antibiotic developed for treatment and prevention of BRD.^{9,11,12} Studies of the pharmacokinetic and pharmacodynamic properties of

gamithromycin showed that a single subcutaneous dose at 6 mg/kg provides rapid and persistent therapeutic activity in the control and prevention of infections, owing to the low level of plasma protein binding and high availability of the drug in lung tissue.¹¹ Gamithromycin is licensed in the European Union and Canada for therapeutic and preventative treatment of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (previously *Haemophilus somnus*).¹³

The purpose of the two field studies described here was to evaluate the efficacy of a single treatment with gamithromycin administered subcutaneously at 6.0 mg/kg body weight for control of BRD in calves at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, *Histophilus somni*, and *Mycoplasma bovis* at the time of entry into the feedlot.

MATERIALS AND METHODS

Two randomized, negative(saline)-control, blinded field studies were conducted at feedlot sites in Canyon, Texas (identified here as Texas site) and Oakland, Nebraska (identified as Nebraska site) from December 8, 2008 to December 15, 2008 (Texas site) and from November 15, 2006 to November 25, 2006 (Nebraska site) to evaluate the clinical efficacy of gamithromycin for control of bovine BRD in multi-origin cattle considered at high risk of developing BRD during transport or after introduction to the feedlot. Cattle were obtained from livestock markets and transported to the study sites. Animals within each study were managed similarly and with due regard for their well-being. Animals were handled in compliance with

Merial Institutional Animal Care and Use Committee (IACUC) approvals and all applicable local regulations and requirements of any local IACUC. The study monitors ensured that these procedures were in compliance with the protocol.

Animals

At the Texas site, 308 female calves of crossbred beef breeds, approximately 6 to 10 months of age and weighing 130 to 293 kg each, were purchased from sale barns in Arkansas and transported within 9 hours to the study site (Table 1). At the Nebraska site, 159 calves (68 bulls and 91 steers) of crossbred beef breeds, approximately 6 to 8 months of age and weighing 170 to 256 kg each, were obtained from livestock markets in Kentucky and Tennessee and were transported within 24 hours to the study site (Table 1). For both studies, the day the cattle arrived at the study site was designated Day -1 and processing was carried out the following day (Day 0). Each animal had a uniquely numbered ear tag applied for identification purposes at the time of processing.

Inclusion Criteria

At both study sites, animals that appeared to be in good general health, were not displaying visible signs of BRD or other systemic disease, and satisfied the following criteria were eligible for enrollment in the study:

- A depression score = 0
- Respiratory character score ≤ 1
- Rectal temperatures $<40^{\circ}\text{C}$ (104.0°F)

Despite the absence of these signs at inspection on Day 0, the cattle were considered at high risk for development of BRD because they had been exposed to stresses and conditions that were generally known to predispose cattle to infection by viral and secondary bacterial invaders. The cattle had no history of any vaccinations or antibiotic administration for at least 30 days prior to enrollment.

Exclusion Criteria

Cattle that were debilitated, suffering from systemic disease, including BRD, or were injured, fractious, or otherwise unsuitable,

were excluded from enrollment. Animals with a depression score >1 , OR respiratory score >2 , OR a rectal temperature of $>40^{\circ}\text{C}$ (104.0°F) on Day 0 prior to treatment were excluded from the study. Animals known to have received bacterial vaccines for BRD, had been treated with antimicrobials within 30 days prior to enrollment, or had transit time to the study site in excess of 24 hours were excluded.

Processing

Cattle at the Texas site were received on Day -1 and processed on Day 0. At processing, each animal received a uniquely numbered ear tag. A viral respiratory vaccine (**Reliant**[®]; Merial; Duluth, GA) and a multivalent clostridial vaccine (**Cavalry**[™], Schering-Plough Animal Health; Kenilworth, NJ) were administered to all calves by subcutaneous injection. Ivermectin, an endectocide (**Ivomec**[®] Pour-on, Merial), was administered by topical application. An ionophore (monensin sodium) was included in the ration for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*.

Uniquely numbered ear tags were applied to cattle at the Nebraska site. Each animal received a viral respiratory vaccine (**Bovi-Shield**[®] Gold 5, Pfizer) administered by intramuscular injection and an endectocide, doramectin (**Dectomax**[®] Pfizer) administered by subcutaneous injection.

No antibiotics or vaccines containing antigens/toxins/toxoids of *M. haemolytica*, *P. multocida*, *H. somni*, and/or *M. bovis* were administered at either study site.

Allocation

At each site, Day 0 was the same for all animals. Treatment was assigned to eligible animals by order of processing using a randomization schedule unique for that study site prepared by the biostatistician. To ensure accurate treatment dosing, qualified animals were weighed at each site using a restraint-chute equipped with weigh-scales.

At the Texas site, 308 animals were evenly allocated in a 1:1 ratio (cattle treated with gamithromycin to cattle treated with saline) (Table 1). Animals were assigned to

pens by replicate, with seven replicates per pen.

At the Nebraska site, 159 cattle were allocated in a 2:1 ratio of cattle treated with gamithromycin to animals treated with saline (Table 1). Therefore, each replicate comprised three animals; 53 replicates were formed. Animals were assigned to pen by replicate. Five pens contained 10 replicates and one pen contained three replicates.

Group 1 - Gamithromycin (15.0% w/v) injectable solution (**ZACTRAN**[®]) was administered on Day 0 by subcutaneous injection at 6.0 mg/kg (2.0 mL/50 kg body weight). Group 2 - Sterile saline for injection (0.9% sodium chloride), administered at 2.0 mL/50 kg body weight.

Dosing was calculated by the animal's body weight at processing (Day 0) and to ensure accurate dosing, each dose was verified prior to administration using the dose chart provided in the protocol. Body weights were rounded to the next higher kilogram. Treatments were administered subcutaneously as a single dose on Day 0 in the middle area of the left side of the neck. No more than 10 mL (9.9 mL in the Texas Study) was given in an injection site. Ear tags were used to verify the identity and treatment assignment of each animal.

Animal Management

Outdoor pens at the Texas site had dirt floors and were of standard North American feedlot design. The ration for the cattle consisted of corn/alfalfa hay/cottonseed hulls/corn gluten/trace mineralized salt and contained monensin sodium. Fresh water was available ad libitum from automatic water troughs.

The Nebraska site had outdoor pens constructed of steel pipe with concrete-floors. Animals had free access to feed via feed bunks. The ration consisted of oats, alfalfa, **Sweet Bran 60**[®] (Cargill, Blair, NE), and liquid supplement. Fresh water was available ad libitum throughout the study via automatic waterers.

Blinding

At the Texas site, the Monitor, Investigator,

and person administering treatments knew the treatment assignment of the animals. All other persons performing post-treatment evaluations were not present during treatments and did not have access to the allocation/treatment assignments.

At the Nebraska site, all persons performing post-treatment evaluations were blinded to the treatment of individual animals by not being present during treatments and by not having access to the allocation/treatment assignments. The Monitor, Quality Control person, and person(s) administering treatments knew the treatment assignment of the animals.

Primary Endpoints

Cattle in each treatment group that developed BRD were classified as treatment failures. This classification was based on:

1. Mortality attributed to BRD during the post-treatment period (Days 1 to 10) as confirmed by the presence of bronchopneumonia or BRD on necropsy.
2. Animals displaying clinical signs of BRD defined by the following criteria during the post-treatment period Days 1 to 10
 - A. Depression score > 1, OR Respiratory character score >2, AND Rectal temperature of > 104.0oF
 - B. Respiratory Score = 3 (regardless of rectal temperature); if occurred.
 - C. Depression Score >3 (regardless of rectal temperature); if occurred.

Animals were observed and clinical variables (depression, respiratory character, and rectal temperature) were recorded daily from Days 1 to 10. However, only animals with depression score >1 and/or respiratory character score >2 had their rectal temperatures measured and recorded. As often as possible, observations were performed at approximately the same time of day (morning) per local practice. The following scales for scoring depression and respiratory character were used:

Depression scores

Table 2. Number and percentage of treatment successes in each study

Treatment Group	Texas site		Nebraska site	
	Treatment Successes (%)	P-Value	Treatment Successes (%)	P-Value
Saline Control	90/154 (58.4)	0.002	19/53 (35.8)	0.002
Gamithromycin	120/154 (77.9)*		91/106 (85.8)*	

Treatment successes were determined by the absence of clinical signs of BRD throughout the 10 days after treatment
 * Denotes a statistically significant difference ($p < 0.05$)

- 0 = Normal: Bright, alert, and responsive
- 1 = Mildly Depressed: Stood isolated with its head down or ears drooping, but quickly responded to minimal stimulation.
- 2 = Moderately Depressed: Stood isolated with its head down, showed signs of muscle weakness (standing cross-legged or knuckling when walking). Showed a delayed response to minimal stimulation or required greater stimulation before showing response.
- 3 = Severely Depressed: Recumbent and reluctant to rise, or if standing isolated, reluctant to move. When moving, ataxia, knuckling, or swaying was evident. Eyes dull, head carried low with ears drooping, possible excess salivation/lacrimation.
- 4 = Moribund (recumbent)

Respiratory scores

- 0 = Normal: no abnormal respiratory symptoms were present. Respiratory rate and effort were appropriate for the environment.
- 1 = Mild respiratory distress: serous nasal or ocular discharge and/or cough.
- 2 = Moderate respiratory distress: mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
- 3 = Severe respiratory distress: marked increase in respiratory rate or effort including one or more of the following: open mouth breathing, abdominal breathing, or extended head.

Rectal temperatures were measured and recorded on Day 0 prior to treatment. For the remainder of the study, temperatures were only measured/recorded for those animals with depression score >1 and/or respiratory character score >2.

Other Efficacy Endpoints

Microbiology

Pretreatment nasopharyngeal swabs were taken from cattle at the Texas site on Day 0 before treatment. At both sites, any animals that were removed from the study due to BRD had a nasopharyngeal swab taken on the day they were declared a treatment failure. Swabs were placed in media, maintained on ice packs, and delivered directly to the on-site laboratory the swabs were cultured for *M. bovis* and bacterial pathogens (*M. haemolytica*, *P. multocida*, *H. somni*). Bacterial isolates were maintained at approximately -70°C. Isolates were transferred to Microbial Research, Inc., Fort Collins, CO.

Clinical Adverse Experiences

Animals were observed for clinical adverse experiences (AE) beginning on Day 0 post-treatment and daily thereafter.

Statistical Analysis

The two sites were statistically analyzed independently. At the both sites, individually, the proportion of successes for the two treatments within each pen were analyzed using a generalized linear mixed model with pens considered random. Specifically, the GLIMMIX procedure in SAS® Version 9.1.3 was used with Treatment the only fixed effect and Pen and Pen-by-Treatment interaction the two random effects. The logit link was used for this analysis. The test was conducted using a (two-sided) alpha=0.05 significance level.

RESULTS

Primary Endpoints

The proportion of treatment successes (absence of clinical signs of BRD) in the group treated with gamithromycin was significantly higher ($P < 0.05$) at both sites than in the saline-treated control groups (Table 2). There were no deaths associated with BRD in any group at either site.

At the Texas site, rectal temperatures in cattle classified as treatment failures ranged from 40°C (104.0°F) to 41.9°C (107.4°F) in the gamithromycin group and from 40°C to 41.8°C (107.2°F) in the saline-treated group. At the Nebraska site, rectal temperatures for cattle that were treatment failures ranged from 40°C (104.0°F) to 41.2°C (106.1°F) in the gamithromycin group and from 40°C to 41.3°C (106.4°F) in the saline-treated group.

At both sites, cattle that were deemed treatment failures generally received a respiratory score of 1 at one or more evaluations. A respiratory score of 2 was recorded for nine of the saline-treated cattle at the Texas site that were treatment failures. There were no animals in the gamithromycin group given a respiratory score of 2 at the Texas site. At the Nebraska site, respiratory scores of 2 were recorded for several cattle of both treatment groups at one or more evaluations, irrespective of their BRD status. Depression scores were generally 0 or 1 for all cattle at both sites; however, a depression score of 2 was infrequently recorded in both treatment groups at the Nebraska site.

Secondary Efficacy Endpoints

Microbiology

At the Texas site, 148 of the 158 bacte-

rial isolates collected from nasopharyngeal swabs on Day 0 before treatment and submitted to the central laboratory were viable. The identity of the organisms could be confirmed from 132 pretreatment nasopharyngeal swabs (Table 3). *Mannheimia haemolytica* was isolated from 57 samples and *P. multocida* was isolated from 88 samples. *Histophilus somni* and *M. bovis* were not isolated from any pretreatment samples at the Texas site.

At the Nebraska site, nasopharyngeal swabs were only collected from animals declared treatment failures. *Pasteurella multocida*, *M. haemolytica*, and *M. bovis* were among the organisms isolated from the animals declared treatment failures.

Clinical Adverse Experiences

No adverse experiences were noted for any cattle at either site.

DISCUSSION

Several complex risk factors are involved in the development of BRD, including the animal's susceptibility and the exposure of the cattle to pathogens under stressful conditions.^{4,8,9} BRD remains the most common and the most expensive disease of feedlot cattle in the United States, considering the costs for increased labor, vaccinations, treatments, increased time to reach ideal weight, and death losses.^{2,3,5}

Contributing factors to the immunosuppression of the cattle include transport, which subjects cattle to prolonged exposure to exhaust fumes, time without food or water, and overcrowding. Infectious agents

Table 3. BRD pathogens isolated from pretreatment nasopharyngeal swabs at the Texas site

Treatment Group	<i>Mannheimia haemolytica</i>		<i>Pasteurella multocida</i>	
	Treatment Successes	Treatment Failures	Treatment Successes	Treatment Failures
Saline Control (n=69) ^a	14	14	24	23
Gamithromycin (n=63) ^a	23	6	31	10

Treatment successes and failures were determined at study completion an=the number of animals confirmed positive for BRD pathogens before treatment

of BRD are ubiquitous, and commingling of animals from different sources provides exposure to several infectious pathogens. Environmental and processing risk factors include weather, exposure to dust, humidity, poor ventilation, high stocking density, nutritional changes, and possibly some influence by heritability factors.^{2-5,8,14-16}

Several different approaches have been taken to mitigate the risk and impact of this ubiquitous disease complex. Vaccination of feeder calves against BRD agents has been in practice for many years. However, many studies indicate that the use of vaccines has done little to reduce the incidence of BRD.^{4,10,17} Reasons for the failure of vaccines to be effective in providing a benefit appear are likely multifactorial, but would include immunosuppression due to stress, commingling leading to exposure of cattle at sale barns and in transit, and immunization against all the potential pathogens that could be present is not possible.

Several studies have shown that the therapeutic or prophylactic (metaphylactic) use of antibiotics is indicated for cattle with primary or secondary bacterial infections associated with BRD.^{4,6,12,18-27} Therapeutically, antibiotics are administered to animals showing clinical signs of illness.^{4,19,21,22,24,27} These animals might require repeated antibiotic treatments using a short-acting product or a single injection of a long-acting product that demonstrates activity persistent and sufficient enough to prevent a relapse and to allow lung lesions to heal. Metaphylactically, antibiotics are administered to all animals of a lot on or soon after arrival at the feedlot without determining the status of individual animals beforehand. This approach is often preferred because clinical signs of illness may not be apparent in some cattle. Several studies describing the use of various antimicrobials have demonstrated that the metaphylactic approach to managing BRD in feedlot calves can be beneficial in terms of morbidity and/or mortality reductions.^{4-6,12,20,23,25,26,28,29} However, the historical challenge has been to determine the most

effective timing for metaphylactic treatments.^{23,28,29} There are a number of publications describing metaphylactic antimicrobial therapy with various treatment regimens.

Azalide macrolides are particularly effective for treatment of upper and lower respiratory infections because of their excellent potency against the organisms responsible for those infections and their ability to achieve high concentrations in lung macrophages and in epithelial lining fluid of the bronchioles, where BRD pathogens multiply and cause extensive damage.^{11,30,31} Several macrolide antibiotics, including erythromycin, tylosin, tilmicosin, spiramycin, and tulathromycin are approved for treatment and control of BRD in cattle in the United States and other countries.³¹ Although these compounds are generally well absorbed and reach high concentrations in respiratory and other tissues, many of them bind extensively to plasma proteins, which restricts their extravascular distribution.^{11,30,31} Therefore, some of these antibiotics (eg, erythromycin and tylosin) require multiple doses when used as preventive or therapeutic treatments for BRD.

Gamithromycin is a 15-membered macrolide antibiotic of the azalide sub-class and is currently licensed for treatment and control of BRD pathogens *M. haemolytica*, *P. multocida*, and *H. somni* in Canada and Europe.^{9,11,12} Administered subcutaneously at 6 mg/kg, gamithromycin is well absorbed, and maximum plasma concentrations are reached 1 hour after dosing.¹¹ However, gamithromycin provides more active drug for distribution to lung tissue than other macrolide antibiotics because only 26% of the drug binds to bovine plasma protein.^{9,11} Therefore, plasma concentrations of gamithromycin are poor predictors of its clinical efficacy because distribution into lung tissue is rapid and extensive, reaching peak concentrations by 24 hours after subcutaneous injection. From 1 to 15 days after injection, the ratio of drug in lung tissue to plasma concentration ranged from 247 to 410 times the concentration mea-

sured in plasma. The volume of distribution (24.9 L/kg) after intravenous administration of gamithromycin to cattle is higher than that for erythromycin (0.79 L/kg), tilmicosin (2.65 L/kg), or tulathromycin (11.0 L/kg).¹¹ A single treatment of gamithromycin demonstrates excellent efficacy against BRD pathogens because of the prolonged concentrations in lung tissue resulting from a long elimination half-life (72 hours) in those tissues.^{9,11}

Results of the present studies are in agreement with those obtained in a series of field trials conducted in Italian feedlots.¹² In these Italian studies, evaluations conducted 14 days after processing and treatment revealed morbidity was significantly reduced ($P < 0.0001$) in cattle treated with gamithromycin compared with saline controls. Gamithromycin was also significantly ($P \leq 0.006$) more efficacious than oxytetracycline or tulathromycin in reducing BRD outbreaks in these Italian field trials. Further evidence of the beneficial effect of administering gamithromycin prophylactically was demonstrated in a recent study by Forbes et al⁹, in which cattle were challenged with *M. haemolytica* 10 days, 5 days, or 1 day after a single pre-treatment with gamithromycin at 6 mg/kg. All groups of cattle treated with gamithromycin had significantly lower lung *M. haemolytica* counts and fewer clinical signs associated with BRD infection when compared to controls.

CONCLUSIONS

Based on the fact that cattle in the present field trials had lower clinical scores when treated with gamithromycin at 6 mg/kg than saline treated cattle, it was concluded that the pharmacokinetic and antibacterial properties of gamithromycin provide rapid and prolonged therapeutic and preventive efficacy against the primary pathogens responsible for outbreaks of clinical BRD for at least 10 days after treatment administration.

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