

Efficacy of Tulathromycin versus Enrofloxacin for Initial Treatment of Naturally Occurring Bovine Respiratory Disease in Feeder Calves*

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CLINICAL RELEVANCE

After undergoing arrival processing at one of two commercial feedlots, feeder calves with clinical signs of bovine respiratory disease (BRD) were randomly assigned to receive either tulathromycin (2.5 mg/kg SC) or enrofloxacin (12.5 mg/kg SC). Additional therapy for calves that did not respond to initial treatment followed a prescribed course. Initial treatment with tulathromycin resulted in significantly higher ($P = .009$ and $P = .031$ at sites 1 and 2, respectively) therapeutic success (87.9% and 80%, respectively) than did initial treatment with enrofloxacin (70.2% and 62.5%, respectively). Animals treated with tulathromycin also had fewer subsequent treatments and higher weight gains compared with those treated with enrofloxacin.

INTRODUCTION

In beef feedlots, bovine respiratory disease (BRD) complex is the most common and costly health problem.¹ BRD is a variable complex of disease-causing bacteria and viruses. Organ-

isms most commonly associated with typical shipping fever pneumonia or BRD include *Mannheimia* (*Pasteurella*) *haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*),² and *Mycoplasma bovis*. These bacteria,

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along with a variety of infectious and noninfectious factors that impair pulmonary defenses, lead to initial upper respiratory tract colonization and subsequent lower respiratory tract invasion and pneumonia. During shipment, cattle are often commingled with cattle from other herds with different bacterial and viral flora. This exposure typically occurs in conjunction with shipping-related stress associated with inclement weather, changes in feed and water, and geographic relocation. The combination of shipping, its associated stressors, and exposure to novel bacterial and viral pathogens increases respiratory disease occurrence in recently shipped cattle. Tilmicosin (Micotil 300 Injection, Elanco Animal Health), florfenicol (Nuflo Injectable Solution, Schering-Plough Animal Health), enrofloxacin (Baytril 100, Bayer Animal Health), ceftiofur crystalline free acid (Excede Sterile Suspension, Pfizer Animal Health), and tulathromycin (Draxxin Injectable Solution, Pfizer Animal Health) are the major prescription antimicrobials labeled for treatment of BRD in cattle in the United States.

Tulathromycin was introduced in 2005 for the treatment of BRD caused by *M. haemolyt-*

compared with both tilmicosin and florfenicol. In three field studies with stocker steers,⁴ first-treatment success was significantly higher ($P < .05$), mortalities significantly lower ($P \leq .021$), and average daily gain (ADG) significantly higher ($P \leq .032$) in cattle treated with tulathromycin than for those treated with tilmicosin or florfenicol. In field studies with feeder cattle,⁵ treatment success was significantly higher ($P < .009$) in cattle treated with tulathromycin than in those treated with florfenicol, and treatment success at one of two sites was significantly higher ($P < .018$) in cattle treated with tulathromycin than in those treated with tilmicosin.⁵ The study described here was designed to compare the efficacy of tulathromycin versus enrofloxacin for treatment of naturally occurring BRD in feeder calves at two commercial feedyards.

■ MATERIALS AND METHODS

Animals, Inclusion/Exclusion Criteria, and Arrival Processing

In October and November 2005, calves (age range: 3 to 10 months) were purchased at livestock markets and transported to commercial

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ica, *P. multocida*, and *H. somni* and was recently approved to treat BRD due to *M. bovis*. When administered according to the label at 2.5 mg/kg SC, tulathromycin is rapidly absorbed and widely distributed and provides therapeutic concentrations in bovine lung for an extended period.³ Clinical efficacy of tulathromycin for treatment of BRD, as well as for control of respiratory disease in cattle at high risk of developing BRD, has been well documented in multiple studies.⁴⁻⁶ In previous treatment studies, tulathromycin has been

feedlots in Greeley, Colorado ($n = 806$ mixed-breed steers), or Hereford, Texas ($n = 742$ mixed-breed heifers). Calves had received no known antimicrobial therapy before arrival. Within 24 hours of arrival, all animals at both sites were vaccinated with a modified-live virus vaccine against bovine herpesvirus type 1, bovine viral diarrhea virus (BVDV) types 1 and 2, bovine respiratory syncytial virus, and parainfluenza virus 3 (Bovishield GOLD 5, Pfizer Animal Health) and dewormed (Dectomax Injectable Solution, Pfizer Animal Health); in addition, calves at the

Texas site were vaccinated with a seven-way clostridial vaccine (UltraChoice 7, Pfizer Animal Health). None of the calves received vaccinations against *Pasteurella* or *Mannheimia* spp. General health observations began on the day of processing and continued daily until the allotment was completed.

Beginning the day after processing, calves that exhibited clinical signs of BRD were evaluated for enrollment in the study. Criteria for enrollment included a Clinical Attitude Score (CAS) of 1, 2, or 3 and pyrexia (rectal temperature of 40°C [104.0°F] or higher). The CAS

bial or antiinflammatory therapy, other than that specified in the protocol, after arrival at the study site; had a known history of BRD; had clinical signs of BRD on arrival or at processing; or were evaluated and received a CAS of 4.

At enrollment, an ear notch sample (approximately 1 × 1 cm) was collected from each animal, placed in 10% formalin, shipped to the Veterinary Diagnostic Center (Lincoln, NE), and tested for persistent infection with BVDV. The formalin-fixed ear notches were processed by routine histologic methods, and 4-μm sections were cut from paraffin blocks for im-

At both sites, clinical success was significantly higher for tulathromycin-treated animals.

system is a research tool used to characterize clinical appearance but may not correlate precisely with clinical outcomes. The CAS was assigned according to the following criteria:

- 0 = Normal; bright; alert; responsive
- 1 = Mild depression; signs of weakness usually not present
- 2 = Moderate depression; some signs of weakness; may be reluctant to stand
- 3 = Severe depression; difficulty standing; head lowered or extended
- 4 = Moribund

Calves that met the inclusion criteria were randomly assigned to treatment using a computer-generated randomization plan provided by Pfizer Biometrics. Day 0 for each calf was the day of selection, enrollment, and initiation of experimental treatment. Animals were not eligible for enrollment if they were intact (Colorado) or pregnant (Texas) or had concurrent disease or other physical conditions that might interfere with the progression of BRD or evaluation of response to therapy. Additionally, animals were ineligible if they received antimicro-

munohistochemical staining for BVDV antigen.⁷ Additionally, a nasopharyngeal sample was collected from each enrolled animal using a 7-inch guarded nasal swab (Fisherfinest Transport Swabs, Fisher Scientific, Waltham, MA) in Texas and a double-sided, guarded, mare uterine swab (J273, Jorgensen Laboratories, Loveland, CO) in Colorado. In Texas, samples were placed in a transport medium (Aimes Gel with Charcoal, Fisher Scientific) for shipment; in Colorado, samples were transported on ice to the test facility on the day they were collected. Samples were tested for the presence of *H. somni*, *M. haemolytica*, *P. multocida*, and *Mycoplasma* spp by Microbial Research (Ft. Collins, CO) according to Clinical Laboratory Standards Institute guidelines.⁸

Animals that met enrollment criteria were assigned to treatment according to a randomized complete block design with one animal from each treatment group per block. Blocks consisted of one animal from treatment group 1 (tulathromycin) and one animal from treatment group 2 (enrofloxacin). One hundred twenty-five animals per treatment group were

enrolled during a 3-day period in Colorado and an 18-day period in Texas.

Treatment Administration

To assure and maintain masking, a separate treatment administrator (not the study veterinarian responsible for clinical assessments) administered treatments. Animals were weighed and injected with enrofloxacin^a (12.5 mg/kg [5.7 mg/lb]) or tulathromycin^b 2.5 mg/kg [1.1 mg/lb]). Both medications were within their expiry dates and were administered SC in the right lateral neck. Following treatment, animals were placed in small pens assigned only to enrolled animals.

Clinical Assessments of Enrolled Animals

CAS for each enrolled animal was recorded on days 1 to 28 after treatment. Animals continued to be observed through day 60 (± 3 days), but the CAS was not recorded unless additional treatments were needed. Animals with a postenrollment CAS of 1 or 2 were separated for evaluation; if they did not meet the pyrexia criterion, they were returned to the pen without receiving treatment. Animals with a CAS of 3 or 4, regardless of pyrexia, were classified as nonresponders and were eligible for additional treatment.

Secondary Treatment Administration

Animals were eligible for secondary BRD antimicrobial treatments beginning on day 3 after study enrollment. Animals that met non-responder criteria for the first time were

reweighed and treated with oxytetracycline (Liquamycin LA-200, Pfizer Animal Health; 9.0 mg/lb [20 mg/kg] administered SC in the left lateral neck). Beginning 2 days after oxytetracycline administration, animals that met non-responder criteria a second time were reweighed and treated with florfenicol (18.0 mg/lb [40 mg/kg] administered SC in the left lateral neck). Animals that met nonresponder criteria a third time at least 2 days after treatment with florfenicol were classified as chronics. If additional treatments were indicated, standard feedlot treatment for the study site was followed. The study protocol was not designed to analyze treatment outcomes of subsequent therapies. On days 59 to 63, all animals remaining in the study (including living nonresponders) were weighed.

Statistical Methods

The experimental unit was the animal. The primary assessment of efficacy was analyzed as a binary variable (1 = treatment success; 0 = treatment failure). Animals that responded to initial treatment and did not require secondary treatment were considered a clinical success. The number of animals meeting nonresponder criteria, and therefore eligible for second and third treatments, was counted but not analyzed statistically. Data were analyzed using the GLMMIX macro in SAS with a binomial error and logit link (SAS Institute, Cary, NC). The model included the fixed effect of treatment and the random effects of pen and residual.

Least squares means (LSM) were used as estimates of treatment means. Standard errors of LSM were estimated and 95% CIs were constructed. Back-transformed LSM and CIs were reported.

Weight gain was analyzed using analysis of covariance. The covariate was initial weight. The mixed model included the fixed effect of treatment and the random effects of pen and

^aEnrofloxacin should not be administered to animals intended for dairy or veal production, and animals intended for human consumption must not be slaughtered within 28 days from the last treatment with enrofloxacin.

^bTulathromycin should not be used in female dairy cattle 20 months of age or older, in calves processed for veal, or in animals known to be hypersensitive to the product.

TABLE 1. Back-Transformed Least Squares Means of Animal Response to Treatment, BRD-Associated Chronics and Mortalities, and Weight Gain (Days 0 to 59 or 63)

<i>Parameter</i>	<i>Colorado (days 0–59)</i>		<i>Texas (days 0–63)</i>	
	<i>Tulathromycin</i>	<i>Enrofloxacin</i>	<i>Tulathromycin</i>	<i>Enrofloxacin</i>
No. of animals enrolled	125	125	125	125
No. of animals removed for reasons other than BRD	1 ^a	1 ^b	5 ^c	5 ^d
First treatment success	87.9% ^e (109 of 124)	70.2% ^f (87 of 124)	80.0% ^g (96 of 120)	62.5% ^h (75 of 120)
No. (%) of BRD deaths ⁱ	0 (0%)	0 (0%)	6 (5%)	5 (4.2%)
No. of animals requiring second treatment	11	27	13	27
No. of animals requiring third treatment	4	9	2	9
No. of BRD chronics	0	1	8	9
Weight gain (kg [lb])	82.1 ^j (180.9)	78.5 ^j (173.0)	35.5 ^j (78.1)	32.5 ^j (71.6)

^aMetastatic anaplastic sarcoma.^bSelf-inflicted musculoskeletal injury.^cMusculoskeletal ($n = 2$); protocol deviations ($n = 2$); enteritis ($n = 1$).^dMusculoskeletal ($n = 1$); protocol deviations ($n = 2$); enteritis ($n = 1$); dyspnea not due to BRD ($n = 1$).^{e,f}Different superscripts indicate significantly different values ($P = .009$).^{g,h}Different superscripts indicate significantly different values ($P = .031$).ⁱBRD deaths could appear in the second or third treatment total or in chronics total, depending on the time of death.^jNot significantly different ($P > .05$).

BRD = bovine respiratory disease.

residual. Treatment differences were assessed at the 5% level of significance ($P < .05$). Mortality, CASs, and body weights were summarized for each treatment. Analysis was by site.

RESULTS

Colorado Site

Clinical success (i.e., animals requiring no secondary treatment) for days 0 to 59 was significantly higher ($P = .009$) for tulathromycin-treated animals (87.9%) than for enrofloxacin-treated animals (70.2%; Table 1). Table 1 lists the number of animals eligible for subsequent treatments in each group. A total of 143 thera-

peutic treatments was administered to the tulathromycin group and 172 to the enrofloxacin group. One animal in the enrofloxacin group was declared a chronic. No BRD deaths occurred in either group.

CASs are summarized in Table 2. In general, the percentage of animals with a CAS of 0 to 3 was similar for both treatment groups after day 3.

Enrollment weights ranged from 174.6 to 294.8 kg (385 to 650 lb). Over 59 days, weight gains were numerically greater ($P = .0510$) in tulathromycin-treated animals (82.1 kg [180.9 lb]) than in enrofloxacin-treated animals (78.5 kg [173.0 lb]).

TABLE 2. Percentage of Animals with Clinical Attitude Scores (CASs) of 0 to 3 at Colorado Site

CAS ^a	Day																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Enrofloxacin																		
0	46	62	100	96	91	90	88	93	95	97	98	98	95	98	98	98	98	100
1	42	29	0	4	8	10	10	6	5	3	2	2	4	1	2	2	2	0
2	13	10	0	0	1	0	2	1	0	0	0	0	1	1	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Tulathromycin																		
0	34	56	100	98	92	91	89	94	98	97	98	99	97	100	100	100	100	100
1	47	37	0	2	6	8	10	6	2	3	2	0	3	0	0	0	0	0
2	19	7	0	0	2	0	2	0	0	0	0	1	0	0	0	0	0	0
3	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

^aSee page 129 for an explanation of how CASs were assigned.

TABLE 3. Percentage of Animals with Clinical Attitude Scores (CASs) of 0 to 3 at Texas Site

CAS ^a	Day																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Enrofloxacin																		
0	88	93	93	93	93	93	95	92	94	92	94	100	94	95	97	97	97	95
1	12	6	7	7	6	6	5	8	6	8	6	0	6	5	3	3	3	4
2	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tulathromycin																		
0	88	89	92	94	97	97	97	97	96	98	97	97	97	98	98	99	95	96
1	10	10	8	6	3	3	3	2	4	1	3	3	2	2	2	1	4	4
2	2	1	0	0	0	0	1	1	0	0	0	1	1	0	0	0	1	0
3	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

^aSee page 129 for an explanation of how CASs were assigned.

No adverse events attributable to the experimental treatments were detected after product administration. In the enrofloxacin-treated group, one animal was noted to be lame (toe abscess or injury) and one animal was euthanized subsequent to self-inflicted trauma. In the tulathromycin-treated group, one moribund animal was euthanized (postmortem examination revealed

Day										
19	20	21	22	23	24	25	26	27	28	
94	95	99	99	99	100	100	100	98	99	
6	5	0	1	1	0	0	0	2	1	
0	0	1	0	0	0	0	0	0	0	
0	0	0	0	0	0	0	0	0	0	
98	98	99	99	98	99	100	100	100	100	
2	2	1	1	2	1	0	0	0	0	
0	0	0	0	0	0	0	0	0	0	
0	0	0	0	0	0	0	0	0	0	

Day										
19	20	21	22	23	24	25	26	27	28	
95	97	98	93	93	96	97	99	99	100	
5	3	1	6	5	3	1	0	1	0	
0	0	1	0	0	1	2	0	0	0	
0	0	0	1	2	1	1	1	0	0	
97	97	97	98	99	98	99	99	99	100	
2	1	2	0	1	0	1	1	1	0	
1	1	2	1	0	2	0	0	0	0	
1	2	1	1	0	0	0	0	0	0	

metastatic anaplastic sarcoma), and one animal tested positive for BVDV but did not require additional treatment for BRD and remained with the group throughout the study period.

Texas Site

Clinical success for days 0 to 63 was significantly higher ($P = .031$) for tulathromycin-treated animals (80.0%) than for enrofloxacin-treated animals (62.5%; Table 1). Table 1 lists the number of animals eligible for subsequent treatments in each group. A total of 161 therapeutic treatments was administered to the tulathromycin group and 183 to the enrofloxacin group. Eight animals in the tulathromycin-treated group and nine in the enrofloxacin-treated group were classified as chronics. Mortality associated with BRD was similar for both groups ($n = 6$ in the tulathromycin group; $n = 5$ in the enrofloxacin group).

CASs are summarized in Table 3. During the 28-day clinical observation period, the percentage of animals with a normal CAS (CAS = 0) was higher in the tulathromycin group on 18 of 28 days, the same for both treatment groups on 5 days, and higher in the enrofloxacin group on 5 days.

Enrollment weights ranged from 257.2 to 259.0 kg (567 to 571 lb). Over 63 days, weight gains were numerically greater ($P = .7591$) in tulathromycin-treated animals (35.5 kg [78.1 lb]) than in enrofloxacin-treated animals (32.5 kg [71.6 lb]). No animals tested positive for persistent BVDV infection.

Microbiologic Findings

A total of 248 samples was collected during enrollment at the Colorado site; 37% (81) cultured *M. haemolytica*, 16.6% (41) cultured *P. multocida*, and 1.6% (4) cultured *H. somni*. A total of 247 samples was collected during enrollment at the Texas site; 53% (131) cultured *M. haemolytica*, 10.5% (26) cultured *P. multocida*, and none cultured *H. somni*.

DISCUSSION

At these two sites, cattle that received tulathromycin consistently and significantly had

higher first-treatment BRD success than did those that received enrofloxacin. Fewer animals that received tulathromycin required subsequent treatments than did those that received enrofloxacin, suggesting that tulathromycin provides a more durable BRD cure, and weight gains were numerically higher with tulathromycin than with enrofloxacin. This response to tulathromycin, as measured by the primary variable, first-treatment response, was similar at both locations. Only 12.1% to 20% of animals in the tulathromycin groups failed first treatment, compared with 20% to 37.5% in the enrofloxacin groups. Consequently, the improved first-treatment response reduced the total number of antimicrobial treatments administered. The number of animals requiring subsequent treatments is presented as a numeri-

the two agents. Fluoroquinolones are characterized as rapidly bactericidal. The efficacy of triamides depends on maintaining therapeutic concentrations above the minimum inhibitory concentration of susceptible organisms for sufficient time. In Colorado, cattle that received enrofloxacin had lower CASs on day 1 after treatment than did those that received tulathromycin; however, after that time, CASs were similar for both groups. In Texas, cattle in both groups had similar CASs. Many factors influence the rate and magnitude of clinical responses. These data alone do not provide clear guidance on comparative initial CAS responses during therapy but demonstrate improved therapeutic success and fewer subsequent treatments for tulathromycin.

Tulathromycin efficacy and overall clinical

Tulathromycin achieves concentrations in target tissues that are 70-fold higher than achieved in serum.

cal difference but was not evaluated statistically because this study was not powered to analyze secondary treatment outcomes.

There were differences in enrollment time frames between the two locations (3 days in Colorado and 18 days in Texas). Numerous factors could result in different enrollment rates, including cattle source, disease exposure, transport conditions, and local weather. The individuals responsible for evaluation and treatment of the cattle were blinded to the treatments administered and to the allocation and blocking of cattle in the treatment groups, so the cattle were treated similarly at each site.

CASs, especially for the first 3 days after treatment, are of interest because the two therapeutic agents compared in this study represent different antibiotic classes with different mechanisms of action; consequently, clinical responses to treatment could differ between

performance are supported in other studies.⁴⁻⁶ Tulathromycin achieves concentrations in target tissues that are 70-fold higher than achieved in serum; furthermore, the concentration tends to remain in the lungs.³ Recent studies have shown that tulathromycin significantly reduces mortality and lung lesions in cattle if given as long as 9 days before experimental intratracheal inoculation of *M. haemolytica*.⁹ In a companion study, cattle with naturally occurring BRD were treated with tulathromycin with no additional treatments allowed for intervals of 7, 10, and 14 days.⁹ There was no difference in first-treatment response rate, mortality, or weight gain in the three groups. These two studies provide experimental and clinical evidence that tulathromycin exerts a clinical effect against BRD in cattle for 7 days and perhaps much longer.⁹

Clinical effect in response to bacterial pneumonia is also a function of antimicrobial spec-

trum of activity, as most cases of bacterial pneumonia are the result of a mixed bacterial infection. Recent studies indicate the two most common microbial agents associated with non-responsive BRD are *M. bovis* and BVDV.^{10,11} Tulathromycin has demonstrated efficacy against *M. bovis* and, in the United States, is labeled for treatment of BRD due to *M. bovis*¹² in addition to the other three major bacterial causes of BRD.

CONCLUSIONS

Initial treatment of BRD in feedlot calves with tulathromycin (2.5 mg/kg SC) resulted in significantly higher first-treatment success than achieved with enrofloxacin; in addition, fewer second and third treatments were necessary and higher weight gains were achieved in the tulathromycin group than in the enrofloxacin group during the first 59 to 63 days in this study conducted at two commercial feedlots. The improved clinical response observed with tulathromycin compared with the contemporary positive control is consistent with reports comparing tulathromycin with tilmicosin and florfenicol. The antimicrobial spectrum and pharmacokinetics of tulathromycin in cattle provide measurable clinical advantages as demonstrated in this clinical trial.

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