

Clinical efficacy of gamithromycin versus florfenicol for the treatment of undifferentiated fever in winter-placed feedlot calves

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Abstract

A study was conducted in Alberta, Canada utilizing 4 commercial feedlots to compare the clinical efficacy of gamithromycin to florfenicol for the initial treatment of undifferentiated fever (UF) in winter-placed feedlot calves. There were no significant differences ($P>0.05$) in UF relapse rates and crude case fatality or bovine respiratory disease/histophilus fatality rates between the 2 treatment groups. As a result, the cost-benefit of gamithromycin versus florfenicol was based on the difference in treatment cost between the 2 drugs. Using current market prices and a treatment weight of 750 lb (340 kg), gamithromycin had an economic advantage of \$11.52 CAN per head over florfenicol.

Key words: bovine, BRD, undifferentiated fever, gamithromycin, florfenicol

Résumé

Une étude a été menée en Alberta, Canada, dans quatre parcs d'engraissement commerciaux afin de comparer l'efficacité clinique de la gamithromycine par rapport au florfénicol pour le traitement initial de la fièvre indifférenciée chez des veaux pré-engraissés placés dans des parcs en hiver. Il n'y avait pas de différence significative ($P>0.05$) entre les deux groupes de traitement dans le taux de rechute de la fièvre indifférenciée et le taux brut de létalité ou dans le taux de létalité relié aux maladies respiratoires bovines ou à l'*Histophilus*. Par conséquent, l'analyse coût-bénéfice de l'utilisation des deux médicaments a été faite en considérant la différence dans le coût relatif du traitement avec les deux drogues. En utilisant les prix courants du marché et un poids au traitement de 750 lb (340 kg), l'utilisation de la gamithromycine rapportait 11,52\$ CAN de plus par tête que le florfénicol.

Introduction

Various therapeutic antimicrobials are licensed and available to bovine practitioners to treat bovine respiratory disease (BRD) and undifferentiated fever (UF) in feedlot cattle.^{2,8,10,11,12,13,16} Gamithromycin, an azalide 15-membered semi-synthetic macrolide antibiotic, became available in Canada for the control and treatment of BRD in feedlot cattle a few years ago. There is little published scientific data from controlled field trials in commercial feedlots in North America on the therapeutic efficacy of this macrolide,^{5,9} and no peer-reviewed published comparative clinical efficacy data to other commonly used therapeutic antimicrobials for the treatment of BRD.

The purpose of this field trial was to compare the clinical efficacy of gamithromycin to florfenicol as an initial drug for treatment of undifferentiated fever in winter-placed feedlot calves which did not receive a metaphylactic antimicrobial at feedlot arrival.

Materials and Methods

Study Facility

This trial was conducted during the winter and spring of 2012 at 4 commercial feedlots in Alberta, Canada with feeding capacities between 15,000 and 25,000 head. The 4 feedlots were similarly equipped. Approximately 225 animals were housed in feedlot pens with a heated automatic waterer and a concrete feed bunk within the fence line facing a common feed alley. The hospital barn had a roof and concrete floor, and was equipped with a hydraulically operated squeeze chute with weigh scale and chute-side computer with an individual animal health data management and recording system.^a

Cattle were fed rations consisting of barley grain, barley or corn silage, corn-based dried distiller grains

with solubles, and supplement formulated to meet standard nutritional requirements of feedlot cattle. Monensin sodium^b was included in the ration throughout the feeding period to improve feed efficiency and control coccidiosis as per label claims. Tylosin phosphate^c was included in the starter ration to reduce the incidence of liver abscesses as per label claims. All pens of cattle were fed their rations 3 times daily on an *ad libitum* basis using truck-mounted mixers on load cells.

Study Animals

Winter-placed steer calves that arrived from January to April 2012 and were approximately 6 to 10 months of age, with body weights ranging from 700 to 800 lb (318 to 364 kg), were used in this study. These calves were purchased through an auction market or directly from a backgrounding feedlot. The history of these calves prior to feedlot arrival was not known, which is typical for purchased feedlot cattle. Upon arrival at the feedlot, animals were given a modified-live IBR and BVD type 1 & 2 vaccine,^d 8-way clostridial bacterin,^e *Histophilus somni* (HS) bacterin,^f *Mannheimia haemolytica* leukotoxoid vaccine,^f ivermectin,^g and an anabolic implant.^h All processing products were administered as per label dosage and route. No metaphylactic antimicrobials were used at induction processing. All animals were uniquely identified with a numbered feedlot eartag and CCLIA (Canadian Cattle Identification Agency) tag.

Experimental Design

A sample size of 300 treated animals per group would be necessary to provide 80% power and 95% confidence to demonstrate a difference in first UF relapse rate from 20% to 15% between treatments.⁴

The 2 treatments were: 1) gamithromycinⁱ SC at 2.7 mg/lb (6 mg/kg) of body weight, and 2) florfenicol^j SC at 18.1 mg/lb (40 mg/kg) of body weight. Gamithromycin and florfenicol administration was based on the individual weight of the animal in the treatment chute scale.

Cattle meeting the clinical definition of UF were systematically randomized⁶ to 1 of 2 treatment groups as they were pulled from their home pen for treatment. A coin was flipped to determine which drug would be used to treat the first case; thereafter, every other animal in the chute meeting the case definition was treated with the same drug. For example, if the coin toss was such that the first case was treated with drug 1, the second case was treated with drug 2, the third case with drug 1, the fourth with drug 2, and so on. The trial was not blinded because the staff needed to know which trial drug to administer to the cattle. Cattle were returned to their home pen following initial treatment, and were not marked in any way to identify which trial drug they had been given. Thus, pen riders could not identify which initial drug the calves had been given until they were

repelled and their treatment history was shown on the computer; thus, there is most likely little treatment bias.

UF Case Definition

Any animals appearing “sick” based on subjective parameters such as general appearance and attitude, gauntness, reluctance to move, separation from group, and respiratory signs such as rapid or labored breathing, nasal discharge, and coughing were moved to the hospital area of the feedlot for closer observation. Upon presentation at the hospital facility, the rectal temperature of the “sick” calf was taken with an electronic thermometer^k and its identification entered into the feedlot’s chute-side computer with an individual animal health data management system.

A diagnosis of the initial case of UF was made on an animal if the following criteria were satisfied: 1) the case abstract, which appeared on the computer screen, indicated no previous treatment history for UF; 2) there was an absence of clinical signs attributable to organ systems other than the respiratory tract; 3) there were signs referable to the respiratory system such as depression, inappetence, rapid or labored breathing, nasal discharge, or coughing; and 4) animals met the temperature criteria ($\geq 104.0^{\circ}\text{F}$; 40.0°C). If all these criteria were met, then the animal was treated and designated as UF. All treated animals were returned to their home pen the same day of treatment unless they were severely compromised. Compromised animals were those that could not walk back to their home pen due to weakness or severe disease. Severely compromised cattle were either housed in the hospital pen until they could be returned home, or were euthanized. Animals were humanely euthanized as per the feedlot veterinarian’s euthanasia protocol if they were in severe respiratory distress or could not rise by themselves, or were severely emaciated and dehydrated.

Animals treated with gamithromycin or florfenicol were not eligible for additional therapy until 5 days following treatment (i.e. 5-day minimum post-treatment interval [PTI]). The drug-established minimum PTI was the time interval from treatment to possible re-treatment; 5 days was the standard drug PTI used for florfenicol at the participating feedlots. There is no published or previously established minimum drug PTI for gamithromycin in commercial feedlot cattle; thus, the same drug PTI as florfenicol was used for comparative purposes.

A diagnosis of a relapse case of UF (first or second) was made on the individual animal if the following criteria were satisfied: 1) the case abstract indicated previous treatment for UF, 2) there was an absence of clinical signs attributable to organ systems other than the respiratory tract, and 3) there were signs referable to the respiratory system such as depression, inappe-

tence, labored or rapid breathing, nasal discharge, and/or coughing. An animal was considered a relapse for disease regardless of the time interval from previous treatment to subsequent treatment. This case definition of UF relapse rates is typical in western Canadian feedlot medicine and applied research.^{8,12,13} Animals were treated according to the feedlot's standard treatment protocol.

A calf was defined as a chronic if it had been pulled as a third UF relapse. Such individuals were sent to the chronic pen and no further treatment for that disease was administered because it was unlikely to improve the animal's health, and there were concerns about treatment cost and development of antimicrobial resistance. If the calves were moribund at any time, they were humanely euthanized. Calves gaining weight but could not be returned to their home pen because they could not compete for feed and water with their peers were sent to a rail pen for fattening and slaughter.

Animals that died either naturally or were euthanized during the trial period were necropsied by feedlot veterinarians to determine the cause of death. The cause of death was based on gross pathology.

Data Analysis

Data were analyzed using analytical software programs.¹ UF relapse rates were the proportion of UF cases previously pulled.⁸ Crude case fatality was the proportion of UF cases that died for any reason, and BRDHS case fatality was the proportion of UF cases that died from respiratory disease (fibrinous and/or bronchopneumonia) or histophilosis (i.e. myocarditis, pericarditis, endocarditis, pleuritis, arthritis) based on gross necropsy findings.¹⁴

Myocarditis, pericarditis, endocarditis, and pleuritis (without pneumonia) are classic lesions observed in histophilosis.¹⁴ Arthritis, with or without bronchopneumonia, may be caused by *H. somni*⁶ and/or mycoplasma bacteria,¹ but for the purposes of this study it was included in the category BRDHS since this syndrome may be caused by *H. somni*, and both microorganisms are potentially responsive to the antimicrobials being tested here.⁵

Differences in UF relapse rates and case fatality rates between gamithromycin and florfenicol treatments were analyzed using generalized linear mixed modeling techniques (PROC GLIMMIX) to account for the clustering of calves within pens and feedlot, with both variables treated as random effects. A binomial data distribution and logit link function were used in the modeling procedure. Calculation of Wald-type confidence intervals was done by using pseudo-likelihood estimation. The parameter estimates and confidence intervals were converted to relative risks as previously described.⁷ Individual animals were the unit of analy-

sis. The 5% level of statistical significance ($P \leq 0.05$) was used for all tests.

Multivariable quantile regression analyses were completed (PROC QUANTREG)¹ to compare the median days between initial treatment and first UF relapse and median days between first and second UF relapses between each treatment group. Clustering of calves within pens and feedlots was accounted for by including each variable as a fixed effect in all models. Random effects are not allowed in the quantile regression procedure, which is why pen and feedlot were accounted for as fixed effects. Parameter estimates and 95% confidence intervals were estimated using an interior point algorithm and the Markov chain marginal bootstrap method, respectively. The significance of each factor was assessed using both Wald and Likelihood ratio tests.

Results and Discussion

A total of 602 animals were allocated to the trial. The final data set contained 297 animals in the gamithromycin treatment group and 305 animals in the florfenicol treatment group. A few animals were removed from the final data analysis because the PTI or treatment protocol was not followed, data were not recorded correctly, or the animals did not meet the definition of UF. It is unlikely that these removals biased the overall trial results given the large sample size. In those animals removed, there was no difference in the UF repull or mortality rate between the 2 treatment groups (data not shown).

Randomization was used to ensure that calves allocated to the 2 treatment groups were as similar as possible, in terms of case severity, to reduce potential bias. Clinical scoring of disease severity is not typically used in a commercial feedlot to determine which therapeutic drug to administer to cattle; thus, this variable was not used in this study to allocate calves to treatment group. There were no significant differences in initial rectal temperature of the calves allocated to the gamithromycin group (105.1°F; 40.6°C) or the florfenicol group (105.1°F; 40.6°C), supporting the assumption that the 2 populations were similar in disease severity.

Results are presented in Table 1. There were no statistically significant differences ($P > 0.05$) between gamithromycin and florfenicol in UF relapse rates, crude case fatality rates, BRDHS case fatality rates or post-treatment intervals. In the gamithromycin group, 8 animals died from BRDHS; viz 3 from chronic pneumonia, 1 from fibrinous pneumonia, 1 from bronchopneumonia, 1 from pericarditis, and 2 from arthritis. In the florfenicol group, 8 animals died from BRDHS; viz 3 from chronic pneumonia, 1 from fibrinous pneumonia, 3 from bronchopneumonia, and 1 from arthritis.

The median days between initial treatment and first UF relapses was 21 days for gamithromycin and

Table 1. Clinical efficacy of gamithromycin versus florfenicol in the treatment of undifferentiated fever (UF) in winter-placed feedlot calves.

Outcome	Experimental group		Rel. risk	95% CI	P
	GAM	FLOR			
Number of UF	297	305			
1st UF relapse	50 (17%)	60 (20%)	0.85	0.69-1.20	0.323
2nd UF relapse	17 (34%)	21 (35%)	0.97	0.90-1.74	0.837
3rd UF relapse	1 (5.9%)	1 (4.8%)	1.01	0.87-1.18	0.856
Crude CFR ^a	9 (3.0%)	13 (4.3%)	0.71	0.40-1.66	0.413
BRDHS CFR ^b	8 (2.7%)	8 (2.6%)	1.05	0.49-2.84	0.914

GAM = gamithromycin

FLOR = florfenicol

^athe proportion of UF that died

^bthe proportion of UF that died from bovine respiratory disease and histophilosis (viz chronic pneumonia, fibrinous pneumonia, bronchopneumonia, myocarditis, pericarditis, arthritis)

24 days for florfenicol ($P=0.38$). The median days between first and second UF relapses was 12 days for the gamithromycin group and 13 days for the florfenicol group ($P=0.88$). In this study, relapses were defined as any retreatment of UF, regardless of the time interval between initial treatment and subsequent retreatment following the minimum set PTI of 5 days for the therapeutic drugs being tested. It is not known with certainty when an animal is repulped for retreatment of UF whether it is actually a new occurrence of UF or failure of previous treatment. In western Canada, a proportion of UF cases are not respiratory disease but septicemia from histophilosis, and the time interval from initial treatment to retreatment and/or fatal disease can be quite long.¹⁴

Failure to see differences between the 2 drugs in UF morbidity and case fatality rates suggests that these 2 antimicrobials performed equally in winter-placed calves in western Canada at low to moderate risk of UF which had not been given a metaphylactic antimicrobial on arrival. Further evaluation of how these 2 antimicrobials would compare clinically in higher disease risk cattle or in cattle where the PTI for the drugs was eliminated or extended beyond 5 days would be beneficial. There is no published feedlot trial data in North America evaluating the clinical efficacy of gamithromycin for treating BRD/UF using different post-treatment intervals.

Macrolide antimicrobials are the most common class of metaphylactic antimicrobial used in fall-placed calves in western Canada that are at medium to high risk of UF.^{3,15} It is possible that using a macrolide or other class of antimicrobial at arrival processing in these winter-placed calves would have influenced the clinical efficacy of gamithromycin when used as the therapeutic drug for initial cases of UF, but there are no published

scientific studies comparing gamithromycin to another class of antimicrobial following macrolide metaphylaxis at feedlot arrival. Feedlot trials have found florfenicol to be more effective than tulathromycin as an initial therapeutic drug following tulathromycin metaphylaxis⁹ and tilmicosin metaphylaxis.¹³ Whether the lower therapeutic efficacy of tulathromycin was due to development of antimicrobial resistance following previous metaphylaxis treatment with a macrolide is not known. Further research is needed to answer these questions, preferably in commercial feedlots using controlled field trials so that the data has both internal and external validity; thus, the results provide objective data for bovine practitioners in decision making.

Conclusions

The cost-benefit between the 2 antimicrobials for initial treatment of UF here was simply the difference in treatment costs between gamithromycin and florfenicol since there were no significant differences in relapse or case fatality rates. Using current market prices and a treatment weight of 750 lb (340 kg), gamithromycin had an economic advantage of \$11.52 CAN per head over florfenicol. Performance and carcass data were not measured on these treated cattle. Possible performance or carcass differences between the treatment groups could influence the relative economic difference between the 2 antimicrobials. Further research is needed to answer this question.

Endnotes

^aDG Professional, ITS Global, Okotoks, Alberta or Fusion, SSG Fusion Ltd, Picture Butte, Alberta

^bBIO AGRI MIX LP, Mitchell, Ontario

^cBIO AGRI MIX LP, Mitchell, Ontario
^dPYRAMID®2+TYPE II BVD, Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario
^eTASVAX® 8, Merck Animal Health Intervet Canada Corp, Kirkland, Ontario
^fSOMNU-STAR Ph®, Novartis Animal Health Canada Inc, Mississauga, Ontario
^gBimectin®, Bimeda-MTC Animal Health Inc, distributed by Vetoquinol Canada Inc, Cambridge, Ontario
^hRevalor S®, Merck Animal Health Intervet Canada Corp, Kirkland, Ontario
ⁱZactran®, Merial Canada Inc, Baie D'urfe', Quebec
^jNuflor®, Merck Animal Health Intervet Canada Corp, Kirkland, Ontario
^kM750 thermometer, GLA Agricultural Electronics, San Luis Obispo, CA
^lSAS™ System for Windows, Release 9.1; SAS Institute, Cary, NC

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¹Sifferman RL, Wolff WA, Holste JE, et al. Field efficacy evaluation of gamithromycin for treatment of bovine respiratory disease in cattle at feedlots. *Intern J Appl Res Vet Med.* 2011;9(2):171-180.

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³ZACTRAN product label.

⁴Kahn, CM. *Merck Veterinary Manual.* 10th edition. 2010:1319.

⁵Van Donkersgoed J, Merrill JK. A comparison of tilmicosin to gamithromycin for on-arrival treatment of bovine respiratory disease in feeder steers. *Bovine Practitioner.* 2012;46(1):46-51.



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INDICATIONS

ZACTRAN is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle. ZACTRAN is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

CONTRAINDICATIONS

As with all drugs, the use of ZACTRAN is contraindicated in animals previously found to be hypersensitive to this drug.

WARNING: FOR USE IN CATTLE ONLY. NOT FOR USE IN HUMANS. KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN. NOT FOR USE IN CHICKENS OR TURKEYS.

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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.

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. bovis* 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. bovis* (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 58%).

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