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Comparison of tilmicosin and gamithromycin for treatment of undifferentiated fever in backgrounded winter-placed feedlot calves

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Abstract

A study was conducted in Alberta, Canada utilizing 2 feedlots to compare clinical efficacy of tilmicosin to gamithromycin for the initial treatment of undifferentiated fever in backgrounded winter-placed feedlot calves. There were no significant differences ($P>0.05$) in undifferentiated fever relapse rates and crude case fatality or bovine respiratory disease/histophilus fatality rates between the 2 treatments. As a result, the cost-benefit was based on the difference in treatment cost between the 2 drugs. Using current drug costs and a treatment weight of 750 lb (340 kg), tilmicosin had an economic advantage of $2.23CAN per head over gamithromycin.

Key words: bovine respiratory disease, undifferentiated fever, tilmicosin, gamithromycin

Résumé

Une étude a été menée en Alberta, Canada, dans deux parcs d'engraissement afin de comparer l'efficacité clinique de la tilmicosine et de la gamithromycine 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 entre les deux traitements ($P > 0.05$) dans le taux de rechute de la fièvre indifférenciée et le taux brut de mortalité ou dans le taux de mortalité relié aux maladies respiratoires bovines ou à l'*Histophilus*. Par conséquent, la rentabilité variait selon la différence reliée aux coûts des deux traitements. En utilisant le coût courant des drogues et un poids de traitement de 750 lb (340 kg), l'utilisation de la tilmicosine réduisait les coûts de 2.23$ CAN par tête par rapport à la gamithromycine.

Introduction

Various therapeutic antimicrobials are used to treat bovine respiratory disease (BRD) and undifferentiated fever (UF) in feedlot cattle.[2,8,9,0,11,12,16] When treatment protocols are designed and updated for feedlot clients, it is incumbent on the bovine practitioner to review the current scientific literature or conduct field trials to determine which antimicrobials work best for their client, taking into account disease risks, drug costs, ease of drug use, and other factors, such as feedlot labor. Gamithromycin became licensed in Canada for control and treatment of BRD in feedlot cattle approximately 2 years ago. There is no published scientific data from controlled field trials in commercial feedlots in North America on the therapeutic efficacy of this macrolide, and no data comparing it to other antimicrobials currently used to treat BRD in feedlot cattle.

The purpose of this field trial was to compare the clinical efficacy of tilmicosin to gamithromycin as an initial drug for treatment of undifferentiated fever in backgrounded winter-placed 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 2 similarly equipped commercial feedlots in Alberta, Canada with feeding capacities of 15,000 and 25,000 head. 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 barns had a roof and concrete floor, and were equipped with a hydraulically operated squeeze chute with weigh scale. Chute-side computers with individual animal health data management system[a] was used for records.

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 rations 3 times daily on an *ad libitum* basis using truck-mounted mixers on load cells.

Study Animals

Backgrounded steer calves used in the study arrived from January through April 2012. These animals were approximately 6 to 10 months of age, and body weights ranged from 700 to 800 lb (318 to 364 kg). These calves were purchased through the auction market or directly from a backgrounding feedlot. The history of these calves prior to feedlot arrival was not known, which is typical in purchased feedlot cattle.

Upon arrival at the feedlot, animals were given a modified-live infectious bovine rhinotracheitis and bovine viral diarrhea virus (types 1 and 2) vaccine, 8-way clostridial bacterin, *Histophilus somni* bacterin, *Mannhemia haemolytica* leukotoxoid vaccine, ivermectin, and an anabolic implant. 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 CCIA (Canadian Cattle Identification Agency) tag.

Experimental Design

The sample size used was 390 animals per treatment group. Based on a historical initial BRD treatment rate of 15 to 20%, the trial had a power of 80% and a 95% confidence interval to show at least an 8% difference in treatment response between the 2 drugs.[d]

The 2 treatments were: 1) tilmicosin[e] SC at 4.54 mg/lb (10 mg/kg) of body weight, and 2) gamithromycin[f] SC at 2.78 mg/lb (6 mg/kg) of body weight. Tilmicosin and gamithromycin administration was based on the individual weight of the animal in the treatment chute scale.

Cattle meeting the clinical definition of UF were systematically randomized 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 drug to administer.

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, runny or snotty nose, 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[g] and its identification entered into the chute-side computer with an individual animal health data management system.[a]

A diagnosis of the initial case of UF (undifferentiated fever) 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° F; $\geq$40° 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, defined as those animals that could not walk back to their home pen due to weakness or severe disease. Cattle that were severely compromised were housed in the hospital pen until they could be returned home; if not, they were euthanized. Severely compromised 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 tilmicosin or gamithromycin were not eligible for additional therapy until 5 days following treatment (i.e. 5-day minimum post-treatment interval (PTI)). Five days was the standard drug PTI used following treatment of cattle with tilmicosin at the participating feedlots. There is no published or previously established minimum drug PTI for gamithromycin in the feedlots participating in this study; thus, the same PTI as tilmicosin 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, inappetence, 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.[3,8,11,14,15] Animals that relapsed were treated according to the feedlot's standard treatment

protocol; all steers that relapsed were treated with the same protocol, regardless of initial therapy.

A calf was defined as a chronic if 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 calves were moribund at any time, they were humanely euthanized. Calves gaining weight that could not be returned to their home pen because they could not compete with peers for feed and water were sent to a rail pen for fattening and slaughter.

Animals that either died 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 (SAS™ System for Windows, Release 9.1; SAS Institute, Cary, North Carolina, USA). 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.[13]

Myocarditis, pericarditis, endocarditis, and pleuritis (without pneumonia) are classic lesions observed in histophilosis.[13] Arthritis, with or without bronchopneumonia may be caused by *H. somnus*[13] and/or mycoplasma,[1] but for the purposes of this study it was included in the category BRDHS since this syndrome may be caused by *H. somnus* and both microorganisms are potentially responsive to the antimicrobials being tested here.

Differences in UF relapse rates and case fatality rates between tilmicosin and gamithromycin 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 analysis. The 5% level of statistical significance was used for all tests.

Multivariate quantile regression analyses were completed (PROC QUANTREG, SAS Institute) 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. 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 784 animals were allocated to the trial, 393 animals in the tilmicosin group and 391 animals in the gamithromycin group. Results are presented in Table 1. There were no statistically significant differences ($P>0.05$) between cattle treated with tilmicosin or gamithromycin in UF relapse rates, crude case fatality rates, BRDHS case fatality rates or post-treatment intervals. In the tilmicosin group, 6 animals died from BRDHS; specifically, 2 from chronic pneumonia, 2 from fibrinous pneumonia, and 2 from myocarditis. In the gamithromycin group, 8 animals died from BRDHS; 3 from chronic pneumonia, 2 from myocarditis, 1 from endocarditis, 1 from pericarditis, and 1 from arthritis.

The PTI between initial treatment and first UF relapses was 30 days for the tilmicosin group and 42 days for the gamithromycin group (data not shown). The PTI between first UF relapse and second UF relapses was 12 days for the tilmicosin group and 10 days for the gamithromycin group. 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 PTI of 5 days set for the therapeutic drugs being tested. It is not known with certainty when an animal is repulled 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 instead are septicemia from histophilosis, and the time interval from initial treatment to retreatment and/or fatal disease can be quite long.[13]

Failure to see differences between the macrolide drugs in UF relapse and case fatality rates suggests that these two antimicrobials performed equally in backgrounded calves in western Canada at low to moderate risk of UF. It is not known how clinical efficacy of these two antimicrobials would compare in higher-risk cattle, or in cattle where the post-treatment interval for the drugs was eliminated or extended beyond 5 days. The PTI for tilmicosin can be extended from 5 to 7 days without any negative health effects.[4] There is no published feedlot trial data in North America evaluating the clinical efficacy of gamithromycin for treating BRD/UF using different PTIs.

Macrolide antimicrobials are the most common class of metaphylactic antimicrobial used in fall-placed

Table 1. Clinical efficacy of tilmicosin and gamithromycin for the treatment of undifferentiated fever (UF) in backgrounded winter-placed feedlot calves.

	Experimental group				
Outcome	**TIL**	**GAM**	**Rel. Risk**	**95% CI**	***P*-value**
Number of UF	393	391			
1st UF relapse	44 (11%)	44 (11%)	0.99	0.66-1.42	0.98
2nd UF relapse	13 (30%)	10 (23%)	1.30	0.58-1.85	0.47
3rd UF relapse	1 (8%)	2 (20%)	0.40	0.03-1.55	0.41
Crude CFR[a]	14 (3.6%)	13 (3.3%)	1.07	0.50-2.15	0.86
BRDHS CFR[b]	6 (1.5%)	8 (2.1%)	0.74	0.26-2.05	0.58

TIL = tilmicosin
GAM = gamithromycin
[a]the proportion of UF that died
[b]the proportion of UF that died from bovine respiratory disease and histophilosis (specifically, chronic pneumonia, fibrinous pneumonia, myocarditis, pericarditis, endocarditis, arthritis)

calves in western Canada that are medium to high risk of UF.[3,14] It is not known if using a macrolide antimicrobial at arrival processing in these backgrounded winter-placed calves would have affected clinical efficacy of tilmicosin and gamithromycin when used as the therapeutic drug to treat initial cases of UF. There are no published studies comparing the clinical efficacy of tilmicosin as a therapeutic drug to another class of antimicrobial following tilmicosin metaphylaxis at feedlot arrival. A few studies have evaluated the therapeutic treatment success of tilmicosin in calves with or without tilmicosin metaphylaxis and found no difference in the therapeutic treatment success rates between those given tilmicosin on arrival and non-medicated controls.[4,5,6,15] Two feedlot trials found that florfenicol was more effective than tulathromycin as an initial therapeutic drug following metaphylactic treatment with tulathromycin[8] or tilmicosin.[12] It is not known if the lower therapeutic efficacy of tulathromycin was due to development of antimicrobial resistance following previous metaphylactic treatment with a macrolide. 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 cost between tilmicosin and gamithromycin, since there were no significant differences in relapse rates or mortality. Using current market prices and a treatment weight of 750 lb (340 kg), using tilmicosin for therapeutic treatment of UF had an economic advantage of $2.23CAN per head over gamithromycin.

Endnotes

[a]DG Professional, ITS Global, Okotoks, Alberta, Canada
[b]Rumensin®, Elanco, a Division of Eli Lilly Canada, Inc.
[c]Tylan®, Elanco, a Division of Eli Lilly Canada, Inc.
[d]Super Calc 3, IBM PC
[e]Micotil®, Elanco, a Division of Eli Lilly Canada, Inc.
[f]Zactran®, Merial Canada Inc.
[g]M750 thermometer, GLA Agricultural Electronics, San Luis, Obispo, CA

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References

1. Adegboye DS, Halbur PG, Nutsch RG, Kadlec RG, Rosenbusch RF. *Mycoplasma bovis*-associated pneumonia and arthritis complicated with pyogranulomatous tenosynovitis in calves. *J Am Vet Med Assoc* 1996; 209:647-649.
2. Apley, M. Bovine respiratory disease: pathogenesis, clinical signs, and treatment in lightweight calves. *Vet Clin North Am Food Anim Pract* 2006; 22:399-411.
3. Booker CW, Abutarbush SM, Schunicht OC, Jim GK, Perrett T, Wildman BK, Guichon PT, Pittman TJ, Jones C, Pollock CM. Evaluation of the efficacy of tulathromycin as a metaphylactic antimicrobial in feedlot calves. *Vet Ther* 2007; 8:183-200.
4. Carter BL, McClary DG, Mechor GD, Christmas RA, Corbin MJ, Guthrie CA. Comparison of 3-, 5-, and 7-day post-treatment evaluation periods for measuring therapeutic response to tilmicosin treatment for bovine respiratory disease. *Bov Pract* 2006; 40:97-101.

5. Guthrie CA, Rogers KC, Christmas RA, Vogel GJ, Laudert SB, Mechor GD. Efficacy of metaphylactic tilmicosin for controlling bovine respiratory disease in high-risk northern feeder calves. *Bov Pract* 2004; 38:46-53.
6. McClary D, Vogel G. Effect of timing of tilmicosin metaphylaxis on control of bovine respiratory disease and performance in feeder cattle. *Bov Pract* 1999; 33:155-161.
7. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003; 157:940-943.
8. Perrett T, Abutarbush SM, Wildman BK, Fuchs MT, Schunicht OC, Pollock CM, Fenton RK, Jim GK, Guichon PT, Booker CW, Berg J, Roder J, Spire M. A comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in feedlot calves. *Vet Ther* 2008; 9:128-140.
9. Skogerboe TL, Rooney KA, Nutsch RG, Weigel DJ, Gajewski K, Kilgore WR. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated disease in feedlot cattle. *Vet Ther* 2005; 6:180-196.
10. Sweiger SH, Nichols MD. Control methods for bovine respiratory disease in stocker cattle. *Vet Clin North Am Food Anim Pract* 2010; 26:261-271.
11. Van Donkersgoed J, Berg J, Hendrick S. A comparison of florfenicol and flunixin meglumine with tulathromycin for the treatment of undifferentiated fever in fall-placed feedlot calves. *Vet Ther* 2009; 10:78-85.
12. Van Donkersgoed J, Berg J, Hendrick S. Comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in Alberta feedlot calves. *Vet Ther* 2008; 9:275-281.
13. Van Donkersgoed J, Janzen ED, Harland RJ. Epidemiological features of calf mortality due to hemophilosis in a large feedlot. *Can Vet J* 1990; 31:821-825.
14. Van Donkersgoed J, Merrill J, Hendrick S. Comparative efficacy of tilmicosin versus tulathromycin as a metaphylactic antimicrobial in feedlot calves at moderate risk for respiratory disease. *Vet Ther* 2008; 9:291-297.
15. Vogel GJ, Laudert SB, Zimmerman A, Guthrie CA, Mechor GD, Moore GM. Effects of tilmicosin on acute undifferentiated respiratory tract disease in newly arrived feedlot cattle. *J Am Vet Med Assoc* 1998; 212:1919-1924.
16. Wellman NG, O'Connor AM. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. *J Vet Pharmacol Ther* 2007; 30:234-241.

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