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Comparative efficacy of tilmicosin, florfenicol, and florfenicol-flunixin meglumine for treatment of undifferentiated fever in backgrounded winter-placed feedlot calves given tilmicosin metaphylactically on arrival

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Abstract

A study was conducted in 3 feedlots to compare the clinical efficacy of tilmicosin to florfenicol and florfenicol-flunixin meglumine for the initial treatment of undifferentiated fever (UF) in backgrounded winter-placed feedlot calves treated metaphylactically with tilmicosin at arrival processing. No significant differences ($P > 0.05$) were found in UF relapse rates, crude case fatality rates, bovine respiratory disease and histophilus fatality rates, or average daily gain between the 3 groups. The cost benefit of tilmicosin versus florfenicol and florfenicol-flunixin meglumine was based on the difference in treatment cost between the 3 drugs. Using current market prices and a treatment weight of 828 lb (376 kg), the cost of treatment with tilmicosin was $15.85 CAN less per head compared to treatment with florfenicol, and $15.90 CAN per head less than florfenicol-flunixin meglumine.

Key words: BRD, tilmicosin, florfenicol, flunixin, meglumine

Résumé

Une étude a été menée dans trois parcs d'engraissement afin de comparer l'efficacité clinique de la tilmicosine par rapport au florfénicol et à la combinaison florfénicol-flunixine méglumine pour le traitement initial de la fièvre indifférenciée chez des veaux préengraissés placés dans des parcs en hiver qui reçoivent une dose métaphylactique de tilmicosine à leur arrivée au parc. Il n'y avait pas de différence significative ($P > 0.05$) dans le taux de rechute de la fièvre indifférenciée, le taux brut de létalité, le taux de létalité relié aux maladies respiratoires bovines ou à l'*Histophilus* ou dans le gain moyen quotidien entre les trois groupes. L'analyse coût-bénéfice des trois différents traitements a été faite en utilisant la différence reliée au coût des traitements. En utilisant le coût courant des drogues et un poids de traitement de 828 lb (376 kg), l'utilisation de la tilmicosine réduisait les coûts de 15.85$ CAN par tête par rapport au florfénicol et de 15.90$ CAN par tête par rapport à la combinaison florfénicol-flunixine méglumine.

Introduction

Currently 5 different antimicrobials in the macrolide class are available for therapeutic use in cattle to prevent, treat, and control bovine respiratory disease (BRD) in feedlot cattle,[1,6,10-15,18] including tylosin, tilmicosin, tulathromycin, gamithromycin, and tildipirosin. The latter 4 products are approved both for metaphylactic and therapeutic treatment of BRD. A practical question that arises for the feedlot practitioner is whether they should prescribe the same class or same antimicrobial for initial treatment of BRD as that used for metaphylaxis. The concern is whether there is reduced therapeutic efficacy due to potential antimicrobial resistance. Limited clinical data is available from feedlot trials comparing therapeutic efficacy of various antimicrobials following metaphylaxis with the same or different class of antimicrobial.[10,15]

The purpose of this field trial was to compare the clinical efficacy of tilmicosin to florfenicol and florfenicol-flunixin meglumine as the initial drug for treatment of undifferentiated fever (UF) in backgrounded, winter-placed calves treated metaphylactically with tilmicosin at feedlot arrival.

Materials and Methods

Study Facility

This trial was conducted during the winter and spring of 2013 at 3 commercial feedlots in southern Alberta, Canada, with feeding capacities between 15,000 and 25,000 head. Approximately 250 animals were housed in each feedlot pen with a heated automatic waterer, and a concrete feed bunk within the fence line facing a common feed alley. Hospital barns had a roof and concrete floor, and were equipped with a hydraulically operated squeeze chute with a weigh scale and chute-side computer with an individual animal health data management 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 complete diet at 15 mg/lb (33 mg/kg) throughout the feeding period to improve feed efficiency and control coccidiosis. Tylosin phosphate[c] was included at 5 mg/lb (11 mg/kg) in the complete diet to reduce the incidence of liver abscesses. Cattle were fed 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 to April 2013, and were approximately 6 to 10 months of age with body weights ranging from 750 to 850 lbs (341 to 386 kg). The calves were purchased through an auction market or directly from a backgrounding feedlot, and the previous clinical or therapeutic history of the cattle was not known. Upon arrival at the feedlot, animals were administered a modified-live infectious bovine rhinotracheitis virus (IBR) and bovine viral diarrhea virus (BVD) (types 1 & 2) vaccine[d], 8-way clostridial bacterin[e], *Histophilus somni* bacterin[f], *Mannhemia haemolytica* leukotoxoid vaccine[f], ivermectin[g], and an anabolic implant[h]. Tilmicosin[i] was administered at label dosage (4.54 mg/lb SC; (10 mg/kg) metaphylactically to all calves based on the average induction weight of the group of calves being processed. All animals were uniquely identified with a numbered feedlot eartag and Canadian Cattle Identification Agency tag.

Experimental Design

The study treatments were: 1) tilmicosin[i] SC at 4.54 mg/lb (10 mg/kg) of body weight, 2) florfenicol[j] at 18.14 mg/lb (40 mg/kg) of body weight, and 3) florfenicol-flunixin meglumine[k] at 18.14 mg/lb (40 mg/kg) and 1.0 mg/lb (2.2 mg/kg) of body weight, respectively. Each product administered was dosed according to the individual weight of the animal in the treatment-chute scale. All treatment antimicrobials were administered at label dose and route.

Cattle meeting the clinical definition of UF were systematically randomized[7] to 1 of 3 treatment groups as they were removed from their home pen for treatment. The trial was not blinded because animal health staff (i.e. pen riders) who pulled the sick cattle also administered the therapeutic drugs.

Body weights were measured on the processing chute-side scale at arrival and at terminal weight sort, which was approximately 30 to 60 days before slaughter. The chute-side scale was tared every 20 head.

UF Case Definition

Any animals appearing clinically ill, based on subjective parameters such as general appearance and attitude, decreased rumen fill, reluctance to move, separation from group, and respiratory signs such as dyspnea, tachypnea, nasal discharge, and coughing, were moved to the hospital area of the feedlot for closer observation. Upon presentation to the hospital facility, the rectal temperature of the affected calf was taken with an electronic thermometer[l], and its identification was entered into the chute-side computer with an individual animal health data management system[a].

An initial diagnosis 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 associated with respiratory disease, such as depression, nasal discharge, dyspnea, tachypnea, or coughing; and 4) animals met the temperature criteria ($\geq$ 104.0° F; 40° C). If all these criteria were met, the animal was treated and designated as UF. Treated animals were returned to their home pen the same day of treatment unless they were severely compromised. Compromised animals were defined as those 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; the more severe cases were humanely 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 tilmicosin, florfenicol or florfenicol-flunixin meglumine were not eligible for additional therapy until 5 days following treatment (5-day minimum post-treatment interval (PTI)). The post-treatment interval is the time from treatment to

possible retreatment. Five days was the standard drug PTI used for tilmicosin and florfenicol at the participating feedlots.[2]

Diagnosis of a relapse case of UF (first or second) was made on an individual animal if the following criteria were satisfied: 1) the case abstract indicated previous treatment for UF; 2) clinical signs attributable to organ systems other than the respiratory tract were absent; and 3) the animal presented with signs referable to respiratory disease such as depression, inappetence, dyspnea, tachypnea, 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.[10,14,15] Animals were treated according to the feedlot's treatment protocol, which was the same for all 3 treatment groups.

An animal was defined as chronic if it had been pulled as a third UF relapse. These animals were sent to the chronic pen, and no further treatment was given for that disease. If a calf was moribund at any time, it was humanely euthanized. Those 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. These cattle were not removed from the trial or data analysis.

Cattle that died either naturally or were euthanized during the trial period, which was from arrival to terminal weight-sort, were necropsied by feedlot veterinarians to determine the cause of death. The cause of death was based on gross pathology, which is typical in feedlot practice. These animals were not removed from the data analysis.

Data Analysis

Data were analyzed using analytical software programs[m]. UF relapse rates were the proportion of UF cases previously pulled.[10] Crude case fatality rate was the proportion of UF cases that died for any reason, and BRDHS case fatality rate was the proportion of UF cases that died from BRD (fibrinous pneumonia and/or bronchopneumonia) or histophilosis (i.e. myocarditis, pericarditis, endocarditis, pleuritis, arthritis) based on gross necropsy findings.[16]

Differences in UF relapse rates and case fatality rates amongst the 3 treatment groups 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.[9] Individual animals were the unit of analysis. The 5% level of statistical significance ($P < 0.05$) was used for all tests.

Multivariable quantile regression analyses were completed (PROC QUANTREG[m]) to compare the median days between initial treatment and first UF relapse, median days between first and second UF relapses, median days-on-feed when first treated, and median days-on-feed when the animal died or was railed 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.

Body weight at terminal weight sort was shrunk 4%, which is the industry standard to account for rumen fill. Average daily gain was the difference in body weight from arrival to terminal weight sort divided by the days-on-feed. Mixed linear regression models (PROC MIXED) were used to compare the mean weights and average daily gain (ADG) by initial treatment group, while accounting for the clustering of calves in pens as a repeated measures and feedlot differences as a random effect.

The economic difference between the 3 treatment groups was based on the cost of treatment and any statistically significant ($P < 0.05$) health or performance outcome variables.

Results and Discussion

The median day to first treatment for UF following metaphylactic treatment with tilmicosin was 18 days for all 3 treatment groups. The induction body weight and body weight at first treatment for UF were not different between the 3 treatment groups. The average rectal temperature of first-pull UF cases was 104.9° F (40.5° C), which was similar between the 3 treatment groups. There were no statistically significant differences in UF relapse rates, crude case fatality rate, BRD and histophilosis case fatality rate, days-on-feed when died, days-on-feed when railed, post-treatment interval between first and second relapse, or ADG from arrival to terminal weight-sort between treatment groups (Tables 1 and 2).

Other studies have evaluated the therapeutic treatment success of tilmicosin in calves with UF or BRD, with or without tilmicosin metaphylaxis, and found no statistical difference in the therapeutic treat-

Table 1. Comparative health effects of tilmicosin (TIL), florfenicol (FLOR), and florfenicol-flunixin meglumine (FLOR-FL) for treatment of undifferentiated fever in backgrounded winter-placed steers administered tilmicosin metaphylactically at feedlot entry.

Outcome	TIL	FLOR	FLOR-FL	RR	95% CI	P
Number of UF	360	355	361			
First UF relapse	79 (22%)		63 (17%)	1.26	0.93-1.59	0.13
	79 (22%)	68 (19%)		1.14	0.68-1.18	0.36
		68 (19%)	63 (17%)	1.10	0.82-1.53	0.55
Second UF relapse	32 (41%)		17 (27%)	1.54	0.91-1.89	0.08
	32 (41%)	20 (29%)		1.38	0.85-1.67	0.17
		20 (29%)	17 (27%)	1.11	0.73-2.23	0.71
Third UF relapse	0 (0%)	0 (0%)	0 (0%)	-	-	-
Railed	2 (0.6%)		2 (0.6%)	1.00	0.99-1.01	0.98
	2 (0.6%)	9 (2.5%)		0.21	0.05-0.99	0.05
		9 (2.5%)	2 (0.6%)	4.63	1.01-22.0	0.05
Crude CFR*	15 (4.2%)		15 (4.2%)	1.01	0.99-1.03	0.97
	15 (4.2%)	13 (3.7%)		1.14	0.54-2.20	0.72
		13 (3.7%)	15 (4.2%)	0.89	0.46-1.88	0.75
BRDHS CFR†	11 (3.1%)		8 (2.3%)	1.40	0.26-2.05	0.46
	11 (3.1%)	8 (2.3%)		1.36	0.21-2.10	0.50
		8 (2.3%)	8 (2.3%)	1.03	0.41-2.77	0.96
DOF‡ at first treat	18 (11-28)		18 (11-27)			0.35
	18 (11-28)	18 (11-28)				0.56
		18 (11-28)	18 (11-27)			0.30
PTI§ at first relapse	11 (7-15)		22 (9-28)			<0.01
	11 (7-15)	20 (7-32.5)				<0.01
		20 (7-32.5)	22 (9-28)			0.46
PTI‖ at second relapse	10 (6-18)		8 (3-14)			0.74
	10 (6-18)	6 (3-14)				0.08
		6 (3-14)	8 (3-14)			0.67
DOF¶ when died	49 (36-66)		52 (28-66)			0.68
	49 (36-66)	50 (34-66)				0.71
		50 (34-66)	52 (28-66)			0.96
DOF# when railed	122 (109-134)		135 (115-155)			0.98
	122 (109-134)	153 (122-158)				0.94
		153 (122-158)	135 (115-155)			0.75

*number and (proportion) of UF that died
†number and (proportion) of UF that died from bovine respiratory disease and histophilosis
‡median days-on-feed at first BRD treatment (25th percentile to 75th percentile)
§median post-treatment interval between initial BRD treatment and firstst BRD relapse (25th percentile to 75th percentile)
‖median post-treatment interval between first and second BRD relapse (25th percentile to 75th percentile)
¶median days-on-feed when animal died (25th percentile to 75th percentile)
#median days-on-feed when animal was railed (25th percentile to 75th percentile)

ment success rates between those given tilmicosin on arrival and non-medicated controls.[3,4,8,17] One similar trial in western Canada compared the treatment success of tilmicosin to florfenicol in high-risk calves given tilmicosin metaphylaxis.[5] No significant differences in relapse rates were found between the 2 treatment groups. However, contrary to the current study, significantly lower chronicity, wastage, overall mortality, and BRD mortality were found in florfenicol-treated calves than those treated with tilmicosin. Calves treated with tilmicosin had a higher ADG from allocation to re-implant time than those treated with florfenicol. This

Table 2. Comparative performance effects of tilmicosin (TIL), florfenicol (FLOR), and florfenicol-flunixin meglumine (FLOR-FL) for treatment of undifferentiated fever in backgrounded winter-placed steers administered tilmicosin metaphylactically at feedlot entry.

Outcome	TIL	FLOR	FLOR-FL	SEM*	P-value
In-weight (lb)	792		782	5.84	0.08
	792	785		5.87	0.22
		785	782	5.86	0.63
Terminal weight (lb)†	1264		1267	8.70	0.72
	1264	1270		8.71	0.47
		1270	1267	8.70	0.71
ADG (lb/day)‡	3.59		3.63	0.06	0.47
	3.59	3.62		0.06	0.63
		3.62	3.63	0.06	0.81
Weight (lb) at first treatment for UF	836		827	8.65	0.31
	836	833		8.61	0.70
		833	827	8.64	0.54

*standard error of the mean
†body weight shrunk 4% during terminal weight-sort (end of study and follow-up period)
‡average daily gain from arrival until terminal weight-sort

demonstrates the importance of repeating studies, and comparing treatments under differing conditions with cattle of different disease risks.

In 2 feedlot studies, florfenicol was more cost-effective than tulathromycin for initial treatment of UF following metaphylaxis using tulathromycin[10] or tilmicosin.[15] Additional feedlot studies are required to evaluate the comparative therapeutic efficacy of the same and different classes of antimicrobials following antimicrobial metaphylaxis to determine whether treatment effects vary between different age groups of cattle, different disease risks, or over time as macrolides are used longer and more frequently in feedlot cattle.

The post-treatment interval between first pull (allocation) and first UF relapse was significantly longer in the florfenicol and florfenicol-flunixin meglumine treatment groups than in the tilmicosin treatment group. It is possible that florfenicol and florfenicol-flunixin meglumine have a longer therapeutic effect than tilmicosin. The number of animals railed (i.e., sold prior to the normal slaughter date of the pen) varied significantly between the 3 treatment groups, with more animals railed in the florfenicol treatment group than in the other 2 treatment groups. Two animals in the tilmicosin treatment group were railed, 1 with laminitis and 1 injury. Nine animals in the florfenicol treatment group were railed: 1 fractured leg, 2 unthrifty animals, and 6 with pneumonia. In the florfenicol-flunixin meglumine treatment group, 2 bullers were railed. We cannot explain why there were more railers with pneumonia in the florfenicol treatment group, as there were no differences in UF treatments between the 3 groups. Two of the UF railers in the florfenicol treatment group were not considered to be chronic pneumonia cases; they were repulled only once for UF late in the feeding period (days 105 and 112), and were railed after treatment because they were near market weight. It is not known whether these railed animals actually had pneumonia, since they were not followed into the processing plant. Cattle were systematically assigned[10] to treatment group, and we could find no obvious source of bias in treatment allocation where sicker cattle were treated with florfenicol rather than tilmicosin or florfenicol-flunixin meglumine that could explain this difference. There were no significant differences in body weight and rectal temperature at treatment allocation or subsequent UF relapse rates between treatment groups. Additional studies in larger groups of cattle are required to assess this particular outcome to determine if the difference in railers in the present study is a consistent finding or just a spurious effect.

When the cost difference in value of treatment regimens was calculated, the difference in railers between florfenicol-treated cattle and the other 2 treatment groups was not included because of the differences in the number of railers, which could have been a spurious effect. In addition, some economic factors were unavailable, such as final slaughter weight and performance and

carcass data, to assess an economic loss from railers; these cattle were not followed to slaughter and carcass data were not collected. The treatment cost difference for an 828 lb (376 kg) animal (average weight at first UF treatment in this study) using tilmicosin as the reference was $15.85 per head more for florfenicol and $15.90 per head more for florfenicol-flunixin meglumine treatments. This cost difference was based on the difference in cost between the 3 treatment groups, which will likely vary among veterinary clinics and over time. Additional studies may be necessary to evaluate differences in treatment efficacy in case antimicrobial resistance develops secondary to long-term macrolide usage in feedlot cattle.

Conclusions

There were no differences in health performance between treatments. In this study, tilmicosin was a more cost-effective treatment for UF due to differences in the cost of the drugs.

Endnotes

[a]DG Professional, ITS Global, Okotoks, Alberta
[b]Rumensin®, Elanco, a Division of Eli Lilly Canada, Inc.
[c]Tylan®, Elanco, a Division of Eli Lilly Canada, Inc.
[d]PYRAMID®2+TYPE II BVD, Boehringer, Ingelheim (Canada) Ltd., Burlington, Ontario
[e]TASVAX®8, Merck Animal Health Canada Corp, Kirkland, Ontario
[f]SOMNU-STAR Ph®, Novartis Animal Health Canada Corp, Mississauga, Ontario
[g]Bimectin®, Bimedia-MTC Animal Health Inc., distributed by Vetoquinol Canada Inc., Cambridge, Ontario
[h]Revalor XS®, Merck Animal Health Canada Corp, Kirkland, Ontario
[i]Micotil®, Elanco, a Division of Eli Lilly Canada, Inc., Guelph, Ontario
[j]Nuflor®, Merck Animal Health Canada Corp, Kirkland, Ontario
[k]Resflor®, Merck Animal Health Canada Corp, Kirkland, Ontario
[l]M750 thermometer, GLA Agricultural Electronics, San Luis, Obispo, CA
[m]SAS System for Windows, Release 9.2; SAS Institute, Cary, NC

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