PEER REVIEWED

Efficacy of tilmicosin and tildipirosin for on-arrival treatment of bovine respiratory disease in fall-placed feedlot calves in western Canada

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Abstract

A trial was conducted in a commercial finishing feedlot in southern Alberta, Canada using fall-placed steer calves to evaluate the comparative efficacy of metaphylactic treatment with tilmicosin or tildipirosin for control of bovine respiratory disease (BRD). First-pull treatment rates for BRD were significantly lower ($P<0.01$) in calves administered tildipirosin than those administered tilmicosin on arrival. There were no significant differences in BRD relapse rates, overall mortality, or BRD and histophilosis mortality. While calves treated with tildipirosin on feedlot entry had higher average daily gain ($P = 0.006$) and lower dry-matter conversion ($P = 0.007$) at 56 days-on-feed than those treated with tilmicosin, these performance differences were no longer significant ($P > 0.05$) at 146 days-on-feed. Using current drug prices and based on differences in initial BRD treatment rates, tilmicosin had a net economic advantage of $6.85CAN/head to those treated with tildipirosin on arrival.

Key words: bovine, BRD, tilmicosin, tildipirosin, metaphylaxis

Résumé

Un essai clinique a été mené dans un parc commercial d'engraissement de finition du sud de l'Alberta, Canada, avec des bouvillons d'engraissement placés l'automne afin de comparer l'efficacité relative d'un traitement métaphylactique avec la tilmicosine ou la tildipirosine pour contrôler les maladies respiratoires bovines. Le taux de premier traitement pour maladies respiratoires bovines était significativement moins élevé (P<0.01) chez les veaux traités à leur arrivée avec la tildipirosine plutôt que la tilmicosine. Il n'y avait pas de différence significative entre les deux groupes de traitement au niveau du taux de rechute pour maladies respiratoires bovines, du taux de mortalité en général ou du taux de mortalité associé aux maladies respiratoires ou à l'Histophilus. Les veaux traités avec la tildipirosine à leur entrée au parc d'engraissement plutôt qu'avec la tilmicosine avait un gain moyen quotidien plus élevé (P = 0.006) et un taux de conversion des matières sèches moins élevé (P = 0.007) après 56 jours en engraissement. Toutefois, ces différences au niveau de la performance n'étaient plus significatives (P>0.05) après 146 jours en engraissement. En utilisant les prix courants pour ces médicaments et en se basant sur les différences initiales dans le taux de traitement des maladies respiratoires bovines, l'utilisation de la tilmicosine à l'arrivée des veaux rapportait 6,85$ CAN de plus par tête que l'utilisation de la tildipirosine.

Introduction

Various metaphylactic antimicrobials, such as long-acting oxytetracycline, tilmicosin, tulathromycin, and gamithromycin, are used in fall-placed feedlot calves to reduce morbidity and mortality from bovine respiratory disease (BRD) and to improve performance.[1,2,5,7,8,9,11,12] Last year tildipirosin,[a] a new antibiotic, became available in Canada to treat BRD. Tildipirosin is a novel 16-membered macrolide antibiotic labeled for the treatment of BRD and reduction of morbidity associated with BRD caused by *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* during the first 14 days in the feedlot, when administered at the time of arrival. There is no published scientific data on the efficacy of tildipirosin as a therapeutic or metaphylactic drug in commercial feedlots in North America, nor is there any published data from controlled field trials evaluating the efficacy and cost-effectiveness of tildipirosin to other metaphylactic antimicrobials used in commercial feedlots to reduce BRD.

The purpose of this controlled field trial was to evaluate the comparative effectiveness of tilmicosin to tildipirosin administered on arrival to fall-placed calves in reducing morbidity and mortality due to naturally occurring BRD in a commercial feedlot. The secondary objective was to measure performance (average daily gain and dry-matter conversion) of calves administered tilmicosin and tildipirosin on arrival, and to calculate the comparative cost-benefit of the 2 antimicrobials.

Materials and Methods

Study Facility

This trial was conducted at a commercial feedlot in southern Alberta, Canada with a 1-time feeding capacity of 25,000 head. The animals were housed in open dirt-floor pens with a heated automatic waterer and a concrete feed bunk within the fence line, facing a common feed alley. Each pen held approximately 225 animals. The hospital and treatment area of this feedlot was used. The hospital has a roof and concrete floor and is equipped with a hydraulically operated squeeze chute with weigh scale, chute-side computer, and health data management system.[b] Body temperatures were taken with an electronic thermometer.[c]

Cattle were fed rations consisting of barley grain, barley or corn silage, corn dried distiller grains with solubles, and supplement formulated to meet nutritional requirements of feedlot cattle. Monensin sodium[d] (33 ppm, 100% dry matter [DM] basis) was included in the ration throughout the feeding period to improve performance and control bloat and coccidiosis. Tylosin phosphate[e] (11 ppm, 100 % DM basis) was included in the starter ration to reduce liver abscesses. All pens were fed 3 times daily on an *ad libitum* basis using truck-mounted mixers on load cells. Feed intake was recorded by pen, with feed from sick and chronic pens prorated back to the original lot of cattle. The dry-matter content of the ration varied from starter rations (approximately 55% DM) to finishing rations (approximately 77% DM).

Study Animals

Four thousand five-hundred crossbred steer calves approximately 6 to 8 months of age, with an average induction weight of 739 lb (336 kg) were used in this study. All calves had been recently purchased through the auction market system, or direct from the ranch and shipped to the feedlot. These were bawling calves that were recently weaned. The history of the calves was not known, since that information is not typically provided to finishing feedlots in Alberta.

Upon arrival at the finishing feedlot, animals were given a modified-live IBR and BVD type 1 & 2 vaccine,[f] 8-way clostridial bacterin,[g] *Histophilus somni* bacterin,[h] *Mannhemia haemolytica* leukotoxoid vaccine,[h] ivermectin pour-on or injectable,[i] and an anabolic implant.[j] If it was raining or wet snow was falling, the animals within a processing group were treated with an injectable ivermectin rather than the pour-on ivermectin. All animals were uniquely identified with a numbered feedlot eartag and CCIA (Canadian Cattle Identification Agency) tag. Animals were put onto the study within 48 hours after arrival at the feedlot.

Experimental Design

A randomized block design was used. Each block consisted of 2 pens as they were filled. A total of 20 pens or 10 blocks were created. The sample size used here is typical for commercial feedlot trials when assessing metaphylactic drugs or feed additives, and pen is the unit of analysis.[1,11,12]

The 2 treatments were: 1) tilmicosin[k] SC at 4.54 mg/lb (10 mg/kg) of body weight, and 2) tildipirosin[a] SC at 1.82 mg/lb (4 mg/kg) of body weight. Tilmicosin and tildipirosin were administered at arrival regardless of rectal temperature, and no other metaphylactic antimicrobials were given. On-arrival treatment was dosed according to the average weight of animals in that processing group.

Animals administered tilmicosin and tildipirosin were not eligible for additional therapy until 5 days following on-arrival treatment (i.e. 5-day post metaphylactic interval (PMI)). This was the standard PMI used for tilmicosin at this feedlot. There is no published data on the post-metaphylactic interval for tildipirosin; therefore, the same PMI as tilmicosin was used. Moribund animals were euthanized for humane reasons, regardless of time since metaphylaxis.

Animals from both treatment groups pulled and treated for BRD were treated according to the feedlot's standard treatment protocol for BRD. Animals relapsing a third time with BRD were considered chronics; thus, no further treatment was given and they were placed in a chronic pen. Therapeutic drugs were used at label dose with label withdrawals adhered to. Treatment dosages were based on the individual body weight of the sick animal.

Animal Allotment

Experimental animals were selected from large groups of animals arriving at the feedlot from October 22 to November 21, 2012. As new cattle were presented for processing, the calves within each arrival processing group were randomly assigned to 1 of 2 treatment groups using systematic randomization. A coin was flipped to determine which of the feeding pens was tilmicosin or tildipirosin. Then a coin was flipped to determine if the first calf through the chute for a new block of pens went into the tilmicosin or tildipirosin group. Every other animal through the chute went into the same treatment

group. For example, if the coin flip was heads and heads was set for tilmicosin, then the first calf through the chute received tilmicosin, the second calf through the chute received tildipirosin, the third calf through the chute received tilmicosin, and so on until the 2 pens were filled. Calves were processed and individually weighed in the processing chute. The scale in the processing chute was verified with a standard weight and calibrated as necessary prior to processing. After every 20 head, the scale was tared to 0. Calves from the 2 treatment groups were penned separately. Once 2 pens were full (225 animals in each pen), 2 new pens were filled until 20 pens were placed on trial. Each pen was an experimental unit, and each group of 2 pens represented a block. Animals were moved to their home pen and maintained as a unit for the duration of the trial, which was from induction processing until terminal weight sorting approximately 30 to 40 days before slaughter. Feedlot personnel who processed the cattle were different from feedlot personnel who checked the cattle daily for illness.

Observations

Any animals appearing "sick" based on subjective parameters such as general appearance and attitude, gauntness, reluctance to move, separation from group, and signs of respiratory disease, such as nasal discharge, ocular discharge, abnormal respiration, 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 and its identification entered into the chute-side computer.

A diagnosis of the initial case of BRD 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 BRD; 2) there was an absence of clinical signs attributable to organ systems other than the respiratory tract; and 3) animals met the temperature criteria (≥104.0°F; ≥40°C). If all these criteria were met, the animal was treated and designated as UF (undifferentiated fever). Animals not meeting the temperature criteria were treated and designated as NF (no fever). All treated animals (UF and NF) were returned to their home pen the same day of treatment unless they were severely compromised. Cattle that were severely compromised were housed in the hospital pen until they could be returned home.

A diagnosis of a relapse case of BRD was made on individual calves if the following criteria were satisfied: 1) the case abstract indicated previous treatment for BRD (UF or NF) and 2) there was an absence of clinical signs attributable to organ systems other than the respiratory tract. If treatment for BRD was necessary, then 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 relapse. Such individuals were sent to the chronic pen. If a calf was moribund at any time, it was humanely euthanized. Calves gaining weight but could not be returned to their home pen because they could not compete for feed/water with their peers were sent to a railer pen for fattening prior to slaughter. Feed from these cattle was prorated back to their home pen. Animals that died during the trial period were necropsied by feedlot veterinarians to determine the cause of death.

Statistical Analysis

The following data were analyzed on a pen basis from arrival to terminal weight sort: a) BRD initial treatment rate (UF0 and NF0), b) BRD first relapse rate (UF1 and NF1), c) BRD second relapse rate (UF2 and NF2), d) BRD chronicity rate (UF3 and NF3), e) arthritis treatment rate, f) railers, g) crude mortality rate, h) mortality rate for BRD/histophilosis, i) weight gain, j) average daily gain (ADG), k) daily dry matter intake (DDMI); l) dry matter conversion (DMC), and m) days-on-feed (DOF).

Individual body weights at processing, reimplant, and terminal weight sort were imported into a spreadsheet program,[l] and an average weight was calculated for each pen. From the computerized animal health data, proportional rates for BRD treatment, arthritis treatment, railers, overall mortality, and BRD/histophilus mortality were calculated for each pen. Histophilus mortality included death from myocarditis, pericarditis, pleuritis, and arthritis.[10]

Body weights, DOF, DDMI, ADG, and DMC were calculated for each pen at initial reimplant and at terminal weight sort. Reimplant and terminal weight sort body weights were shrunk 4% (i.e. the standard industry practice of reducing chute weights by 4% to account for animal weight attributed to gut fill). Weight gain per pen was the change in average weight from induction to reimplant or terminal weight sort. Average DOF per pen was calculated as the total head days divided by the number of head inducted, ADG per pen was calculated as the reimplant or terminal sort weight minus the total weight inducted divided by the total head days. DDMI per pen was calculated as the total pounds of feed fed divided by total head days (corrected for DM content). DMC per pen was calculated as the total pounds of feed (DM) fed divided by total weight gain.

Data were analyzed using an analytical software program.[m] A randomized complete block analysis of variance was used to compare outcomes between experimental groups.[3] Statistical significance was set at $P \leq 0.05$.

The relative cost-effectiveness of tilmicosin versus tildipirosin as a metaphylactic drug was calculated based on health and performance variables that were statistically different between the 2 experimental

groups. Variables included the feedlot's metaphylactic antimicrobial therapy cost of $16.44CAN for tilmicosin, $27.68CAN for tildipirosin, and an initial BRD therapy cost of $31.34CAN/animal.

Results and Discussion

First-pull treatment rates for BRD were significantly lower ($P<0.01$) in the tildipirosin group than in the tilmicosin group (Table 1). There were no differences in BRD relapse rates or total mortality and BRD/histophilus mortality between the 2 treatment groups. Fall-placed calves treated with tildipirosin instead of tilmicosin on arrival gained an additional 12 lb (5.5 kg) at first reimplant, approximately 56 days-on-feed, but these weight and performance differences were no longer significant at terminal weight sort (Table 2). These findings suggest compensatory gain in the sick calves over time.

Dosing the metaphylactic drug based on the average induction weight of each incoming processing group may have reduced treatment response rates in both the tilmicosin and tildipirosin groups. However, at this feedlot, calves were bought in 100 lb (45 kg) weight groups; therefore, the variability in incoming weight within a processing group of calves was not very large (data not shown), suggesting that averaging the dose of the metaphylactic drug within each processing group likely had little effect, if any, on reducing potential treatment responses in the 2 treatment groups. Since the same average weight calculation was used for dose determination in both treatment groups, there is no directional bias.

A 5-day PMI was used for tilmicosin and tildipirosin in this study since it was the standard PMI used for tilmicosin at this feedlot. Previous work has suggested that the PMI for tilmicosin can be extended from 3 to 7 days with improved treatment success rates.[2] There is no published data to indicate the most efficacious PMI for tildipirosin. Pharmacokinetics of tildipirosin in bovine plasma, lung tissue and bronchial fluid in live, healthy cattle show a long t½ in lung and bronchial fluid, suggesting a longer PMI of 10 and 11 days could be used.[6]

The health crew was not completely blind to the treatment groups because products given to cattle at processing was part of an individual animal's treatment history which would show up in the computer if the animal was pulled and treated for disease. The animals were not visually identified in any way after processing to make it known to pen riders which antimicrobial the cattle had received at processing, so it is unlikely that there was any significant bias from this lack of complete blinding.

The unit of analysis in this study, the pen, could not be maintained as a unit from arrival until slaughter.

Table 1. Health effects of tilmicosin versus tildipirosin on-arrival metaphylaxis in fall-placed feedlot steer calves.

Variable	Tilmicosin[a]	Tildipirosin[b]	SEM	*P*-value
No. pens	10	10		
No. calves	2250	2250		
BRD – 1st pulls (%)	30	16	0.01	<0.01
- UF[c]	27	15	0.01	<0.01
- NF[d]	3	1	0.003	0.003
BRD – 1st repulls (%)	14	17	0.01	0.30
- UF	13	16	0.01	0.16
- NF	12	0	0.04	0.05
BRD – 2nd repulls (%)	34	27	0.06	0.44
- UF	34	27	0.06	0.41
- NF	10	0	0.05	0.05
BRD – chronics (%)	1.7	1.8	0.005	0.90
- UF	1.7	1.8	0.006	0.90
- NF	0	0	-	-
Arthritis (%)	1.5	1.2	0.003	0.54
Total mortality (%)	1.6	1.3	0.003	0.56
BRD/histophilosis mortality (%)	0.9	0.9	0.002	1.0

[a]Micotil, Elanco Animal Health, Guelph, Ontario, Canada
[b]Zuprevo, Merck Animal Health Intervet Canada Corp., Kirkland, Quebec, Canada
[c]UF = undifferentiated fever (rectal temperature ≥ 104°F [40°C] with clinical signs of respiratory disease)
[d]NF = no fever (rectal temperature < 104°F [40°C] with clinical signs of respiratory disease)

Table 2. Performance effects of tilmicosin versus tildipirosin on-arrival metaphylaxis in fall-placed feedlot steer calves.

Variable	Tilmicosin[a]	Tildipirosin[b]	SEM	*P*-value
No. pens	10	10		
No. calves	2250	2250		
Induction weight (lb)	739	739	1.03	0.84
Reimplant				
- DOF[c]	56	56	-	-
- Weight (lb)	897	908	2.53	0.01
- Weight gain (lb)	158	170	2.33	0.006
- DDMI[d] (lb)	14.7	15.2	0.12	0.06
- ADG[e] (lb/day)	2.82	3.03	0.04	0.006
- DMC[f]	5.28	5.04	0.05	0.007
Terminal sort				
- DOF	146	146	-	-
- Weight (lb)	1247	1246	2.55	0.75
- Weight gain (lb)	508	509	2.19	0.64
- DDMI (lb)	19.3	19.3	0.07	0.93
- ADG (lb/day)	3.35	3.35	0.03	0.98
- DMC	5.77	5.77	0.05	0.99

[a]Micotil, Elanco Animal Health, Guelph, Ontario, Canada
[b]Zuprevo, Merck Animal Health Intervet Canada Corp., Kirkland, Quebec, Canada
[c]DOF = days-on-feed
[d]DDMI = daily dry matter intake
[e]ADG = average daily gain
[f]DMC = dry matter conversion

This study was discontinued at terminal weight sort due to mixing of cattle into different pens prior to sale to reduce carcass discounts. However, it is unlikely that following the cattle through the feeding period to slaughter would have changed the health results observed given that most BRD occurred early in the feeding period. It is not known, or previously reported elsewhere, if performance differences observed between treatment groups at terminal weight sort would have been smaller or larger with another 30 to 40 days-on-feed. Additionally, the comparative differences in tilmicosin and tildipirosin metaphylaxis effect on carcass merit remains unknown. Given the differences observed between the 2 treatment groups were only in initial BRD treatments and there were no differences observed in relapses, mortality or performance at terminal weight sort, it is unlikely that there would have been significant differences in carcass weight and yield and quality grades.[4] Additional studies are warranted in different disease risk, fall-placed feedlot calves with follow-up through to slaughter in order to accurately determine the overall benefit of using tilmicosin versus tildipirosin metaphylactically at induction processing.

The economic advantage of using tilmicosin at arrival processing was $6.85CAN/head compared to using tildipirosin. Changes in disease risks and drug pricing will affect the net economic value of using tilmicosin versus tildipirosin as a metaphylactic drug in fall-placed feedlot calves.

Conclusion

Compared to tilmicosin, metaphylactic treatment with tildipirosin reduced first-pull treatments by 14 percentage points in fall-placed feedlot calves. There were no significant differences in BRD relapses, arthritis treatments or performance between the 2 treatment groups. The net economic advantage of tilmicosin compared to tildipirosin metaphylaxis was $6.85CAN/head, due mainly to the large difference in drug price of the 2 metaphylactic antimicrobials.

Endnotes

[a]Zuprevo, Merck Animal Health
[b]DG Professional, ITS Global, Okotoks, Alberta
[c]M750 thermometer, GLA Agricultural Electronics, San Luis Obispo, CA
[d]BIO AGRI MIX LP, Mitchell, Ontario
[e]BIO AGRI MIX LP, Mitchell, Ontario
[f]PYRAMID®2+TYPE II BVD, Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario

[g]TASVAX® 8, Merck Animal Health Intervet Canada Corp, Kirkland, Ontario
[h]SOMNU-STAR Ph®, Novartis Animal Health Canada Inc, Mississauga, Ontario
[i]Bimectin®, Bimeda-MTC Animal Health Inc, distributed by Vetoquinol Canada Inc, Cambridge, Ontario
[j]Revalor S®, Merck Animal Health Intervet Canada Corp, Kirkland, Ontario
[k]Micotil®, Elanco, A Division of Eli Lilly Canada Inc.
[l]Microsoft Office Excel, Microsoft Corporation, One Microsoft Way, Redmond, WA
[m]Statistix 9 Analytical Software, Tallahassee, FL

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