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Comparison of tildipirosin and tulathromycin for control of bovine respiratory disease in high-risk beef heifers

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Abstract

The purpose of this study was to compare the effectiveness of tildipirosin (TIP) to tulathromycin (TUL) administered at arrival to reduce morbidity in beef heifers (Charolais; n = 785; age = 11.1 ± 1.9 months; average body weight = 830.9 ± 78.48 lb (376.9 ± 35.6 kg)) at high risk of developing bovine respiratory disease (BRD). BRD morbidity was lower in the TIP group (TIP = 6.8%; TUL = 20.9%; $P < 0.01$) over the feeding period. Animals in the TIP group had greater average daily gain compared to heifers in the TUL group (TIP = 2.49 lb (1.13 kg); TUL = 2.34 lb (1.06 kg); $P < 0.01$). No differences were observed between groups for number and severity of lung lesions. In the present study, tildipirosin was more effective than tulathromycin in reducing BRD morbidity and improving growth performance in newly received beef heifers considered at high risk for BRD.

Key words: beef cattle, bovine respiratory disease (BRD), risk assessment, tildipirosin, tulathromycin

Résumé

Le but de cette étude était de comparer l'efficacité de la tildipirosine (TIL) et de la tulathromycine (TUL) administrée à l'arrivée pour réduire la morbidité des taures de boucherie récemment reçues (Charolais; n = 785; âge = 11.1 ± 1.9 mois; poids corporel moyen = 830.9 ± 78.48 lb (376.9 ± 35.6 kg)) à haut risque pour le complexe respiratoire bovin. La morbidité associée au complexe respiratoire bovin était moins élevée dans le groupe recevant la tildipirosine (TIP = 6.8%; TUL = 20.9%; $P < 0.01$). Les animaux dans le groupe recevant la tildipirosine avait un gain moyen quotidien plus élevé que dans l'autre groupe (TIP = 2.49 lb (1.13 kg); TUL = 2.34 lb (1.06 kg); $P < 0.01$). Il n'y avait pas de différence entre les deux groupes pour le nombre et la sévérité des lésions pulmonaires. La tildipirosine s'est montrée plus efficace dans cette étude que la tulathromycine en réduisant la morbidité associée au complexe respiratoire bovin et en augmentant la croissance chez les taures de boucherie nouvellement arrivées et considérées à haut risque pour le complexe respiratoire bovin.

Introduction

Bovine respiratory disease (BRD) is the primary health problem in the beef cattle industry worldwide, and has serious animal welfare impact and causes economic loss.[5,10,12] Incidence of this multifactorial disease is closely related to predisposing factors, including the immune status of young cattle, severity of stressful events, environmental characteristics, facilities, and previous health management.[10]

The Italian beef system is based on fattening young calves imported from abroad, especially from France. Cattle are inevitably subject to stressful transport conditions, which last on average 8 to 12 hours. To meet customer demand, imported animals are more often females, very young, and lightweight. These animals may not be fully immunocompetent, and therefore more susceptible to BRD. Even under excellent management conditions and administration of well-designed immunization protocols, preventive antimicrobial treatment is often required to reduce morbidity and mortality due to BRD in high-risk cattle.[8] The purpose of this study was to evaluate the effectiveness of tildipirosin and tulathromycin administered to newly received beef heifers at high risk of BRD for reducing morbidity and mortality under field conditions, and to determine whether there were differences in the incidence and severity of lung lesions.

Materials and Methods

Animals

A total of 785 Charolais heifers (average live weight 830.9 ± 78.48 lb (376.9 ± 35.6 kg)), with an average age of 11.1 ± 1.9 months, were imported from France and enrolled in the study. The study was conducted at a commercial finish-feeding operation located in northern Italy that formally consented to conduct the research. Animals enrolled were considered to be at high risk of developing undifferentiated BRD.

Risk for developing BRD was evaluated using an assessment system developed by the University of Milan in collaboration with MSD Animal Health[13]. This system leads to a risk evaluation associated with the characteristics of the animal (sex, breed, live body-weight, transport information, health, and previous management at the farm of birth), and rearing environment that could impact morbidity. The overall risk range is from 0 to 264 points, and scores above 150 are considered high risk. The score is obtained by adding the risk related to the animal characteristics (from 48 to 136) to the risk associated with management (from -28 to +69), structures (from -10 to +33), and feeding (from -10 to +26). The overall animal BRD risk score for animals enrolled in the trial was 163, which was determined by adding the score for high-risk animals (101) to the combined score for being raised under high-stress conditions (management score +35; structure score +18; feeding score +9).

Processing

Animals were processed within 24 hours of arrival at the feedyard. All animals were identified by individually numbered ear tags. Heifers were weighed and treated for internal and external parasites with ivermectin[a] administered subcutaneously at 90.72 µg/lb (200 µg/kg) of body weight. Animals were vaccinated with a combination bovine herpesvirus-1, bovine viral diarrhea, parainfluenza-3, and bovine respiratory syncytial virus vaccine[b]. No other vaccines or bacterin/toxoids were administered. Animals arrived on different days, were grouped in pairs based on order of entry, and randomly allocated within pair to receive either tildipirosin[c] (TIP; n = 398) at 1.81 mg/lb (4 mg/kg) or tulathromycin[d] (TUL; n = 387) at 1.13 mg/lb (2.5 mg/kg). Animal body weight (BW) obtained at processing was used for dose determination. Treatments were administered subcutaneously in the neck in front of the shoulder, with a maximum volume of 10 mL per injection site. Treatments were administered by the investigator at the time of processing. Individual animals from each processing group were systematically randomized to 1 of 2 matched pens, where they remained until harvest. A randomized block design was used with pen as the unit of analysis. Each block consisted of 2 pens, 1 from each experimental group (TIP and TUL). There was an average of 20 animals per pen.

Housing

Heifers were penned in open-sided sheds; approximately half of the heifers were housed on straw bedding and half on slatted floors during the feeding period. Animals were provided *ad libitum* access to rations formulated to meet or exceed the requirements established by the National Research Council[9] for maintenance and expected growth. Dry matter intake was not recorded. According to European Union legislation,[11] no growth promoters or hormones were administered. All animals had *ad libitum* access to water.

Observations

General health evaluations were conducted daily in the pens through the entire feeding period by a veterinarian and qualified animal health-care personnel who were blinded to treatments. Signs of abnormal respiration and depression were categorized according to predefined criteria as absent, mild, moderate, or severe (Table 1), and recorded. Rectal temperature was measured in animals with mild to severe signs of abnormal respiration and depression. Sick animals were treated according to the standard facility protocols, and returned to their study pens. Morbidity due to BRD was defined

Table 1. Categorization of clinical signs of BRD for respiration and depression.

Clinical sign	Presence/severity of clinical signs			
	Absent	**Mild**	**Moderate**	**Severe**
Respiration	Normal rate and character	Slightly increased rate and/or slightly abnormal character	Moderately increased rate and/or abnormal character	Severely increased rate and markedly abnormal character (may exhibit open-mouth breathing)
Depression	Bright, alert, and responsive; normal appetite/abdominal distension (rumen fill)	Reduced responsiveness; decrease appetite	Depressed; able to stand unassisted	Moribund; unable to stand without assistance

as animals showing mild to severe depression and/or respiratory signs and having a rectal temperature ≥104°F (40°C). Animals diagnosed with BRD (first episode) were administered 2 doses of florfenicol[e] at 9.07 mg/lb (20 mg/kg) 48 hours apart. Nasal swabs were taken from 27 treated animals randomly selected during the study in order to identify etiological agents.

To assess performance, average daily gain (ADG) was calculated by subtracting initial individual BW from individual final BW, and dividing by days-on-feed. Data collected at slaughter included cold-carcass weight, dressing percentage, and lung lesions within a subgroup of animals (n = 433; 207 for TIP vs 226 for TUL). Lung scoring, using the Schneider et al[12] protocol, was recorded as: 0 = normal, no lesions observed; 1 = affected area involved less than 1 cranial lobe and less than 5% lung volume; 2 = adhesions, affected area, or both in more than 1 cranial lobe with greater than 5% but less than or equal to 10% of lung volume; 3 = adhesions affecting more than 1 cranial lobe, greater than 10% to less than or equal to 15% lung volume affected, a small portion of lung was missing, or a combination of these; 4 = more than 15% missing lung volume; and 5 = active bronchial lymph nodes. To confirm the inflammatory nature of the lesions, a sample of 16 affected lungs were randomly collected for histological evaluation.

Statistical Analysis

Absolute and percentage frequencies were used for qualitative variables, while mean, standard deviation (SD), minimum, maximum, and median were reported for continuous variables. Continuous variables were analyzed with Student's t-test. Variables expressed on either a binary or ordinal scale were analyzed using the chi-square test. Results are reported as mean differences with 95% confidence limits and probability values for a 2-tailed test. Cumulative BRD morbidity (first episode) during the feeding period was analyzed using the log-rank test and plotted using a Kaplan-Meier curve. All data were analyzed using an analytical software program[f], and statistical significance was set at $P \leq 0.05$.

Results and Discussion

BRD morbidity was lower in the TIP group compared to heifers in the TUL group (6.8% TIP vs 20.9% TUL; $P < 0.01$; Table 2). The cumulative BRD morbidity showed greater efficacy of TIP compared to TUL as shown in the Kaplan-Meier graph (Figure 1), and from the result of the log-rank test ($P < 0.01$). The primary pathogens isolated from nasal swabs were *Pasteurella multocida* (n = 10), *Moraxella* spp (n = 6), and *Histophilus* spp (n = 1). No heifers died during the study.

When analyzing the incidence of BRD in each housing type (Table 3), heifers in the TIL group had lower BRD morbidity than those in the TUL group, both on straw bedding and on slatted floors (on straw bedding TIP = 6.7%; TUL = 18.2%; $P < 0.05$; on slatted floor TIP = 6.8%; TUL 23.9%; $P < 0.01$).

The differences in efficacy between tulathromycin and tildipirosin in this study were possibly due to differences in the pharmacokinetics of the 2 active ingredients. Although tildipirosin and tulathromycin are 2 of the newest macrolides specifically developed for BRD management, the tildipirosin registration dossier reports that it persists in lung tissue above the MIC_{90} for all typical bacterial pathogens for at least 14 days after administration, and up to 28 days with a concentration above 2 µg/mL. Moreover, tildipirosin interacts differently with bacteria ribosomal subunits compared to tulathromycin; the interactions of the piperidine components, which are specific for tildipirosin, indicate how its mode of action is distinct from 15-membered azalide tulathromycin.[1]

At the end of the 125-day feeding period, heifers in the TIP group were heavier ($P < 0.01$) and had 0.15 lb (0.07 kg) greater ADG ($P < 0.01$; Table 2). Similar differences in ADG were observed in heifers treated with TIL or TUL and fed in different housing types, as reported in Table 3 (on straw bedding TIP = 2.62 lb (1.19 kg); TUL = 2.45 lb (1.11 kg); $P < 0.01$; on slatted floor TIP = 2.38 lb (1.08 kg); TUL 2.23 lb (1.01 kg); $P < 0.01$). Similarly, carcasses from heifers in the TIP group tended to be heavier at slaughter ($P = 0.06$), but there was no difference in dressing percentage (Table 4).

The negative impact of BRD on ADG in this study may have been due to lower feed intake; however, dry matter intake was not measured by the cooperating commercial feedlot. Two studies reported that animals suffering from BRD visited the feed bunk less often and spent less time at the bunk compared to healthy calves.[3,14] However, other studies have shown that in the days following treatment, animals went to the feed bunk more often than animals never treated. In some circumstances, this behavior results in compensatory growth, which allows previously morbid calves to close the growth gap.[2,7] Nevertheless, compensatory growth does not always occur, and is strongly influenced by animal age and weight, length of intake restriction, and length of the finishing period. Lighter animals (485 to 595 lb; 220 to 270 kg) appear to be less affected by negative effects of BRD on ADG, possibly because of the longer finishing time to fill the growth gap.[2,6] Results of the current study are consistent with those reported by Burciaga-Robles et al,[5] but in contrast to findings by Fucci et al[5] who reported 2 groups of newly received beef cattle treated with 2 different antimicrobials had significantly different BRD rates, but there were no differences in ADG at the end of a short finishing period.

There were no significant differences between treatment groups in the number of lung lesions or the

Table 2. Morbidity, weight gain, and days-on-feed for feeder heifers treated with tulathromycin or tildipirosin at arrival processing.

Variable	Experimental group		Difference (95 % CI)	*P*-value
	Tulathromycin*	Tildipirosin†		
Age at arrival (months)				
Mean ± SD (N)	11.1 ± 1.97 (387)	11.14 ± 1.92 (398)	-0.08 (-0.45, 0.29)	0.6708
Median (min - max)	10.8 (7.07 - 16.4)	11.1 (7.26 - 17.1)		
Initial BW (lb)				
Mean ± SD	827.40 ± 79.48	836.95 ± 77.62	-9.48 (-20.81, 8.93)	0.4324
Median (min - max)	823.42 (670 - 1164)	837.75 (670 - 1076)		
DOF‡				
Mean ± SD	126.4 ± 8.36	125.51 ± 5.51	0.89 (-0.46, 2.24)	0.1977
Median (min - max)	124 (118 - 174)	125 (102 - 174)		
BRD first pull % (N)	20.9 (81)	6.8 (27)	14.1 (7.5÷19.8)	0.0001
Final BW (lb)				
Mean ± SD	1122.78 ± 102.71	1149.63 ± 107.34	-28.85 (-41.58, -12.13)	0.0004
Median	1118.90	1132.44		
(min - max)	(809.86 – 1518.24)	(883.36 – 1465.02)		
ADG§ (lb)				
Mean ± SD	2.34 ± 0.53	2.49 ± 0.64	-0.15 (-0.24, -0.066)	0.0004
Median (min - max)	2.38 (0.24 - 4.34)	2.47 (-0.15 - 9.74)		

*Draxxin®, Pfizer Italia srl
†Zuprevo®, MSD Italia srl
‡DOF = days-on-feed
§ADG = average daily gain

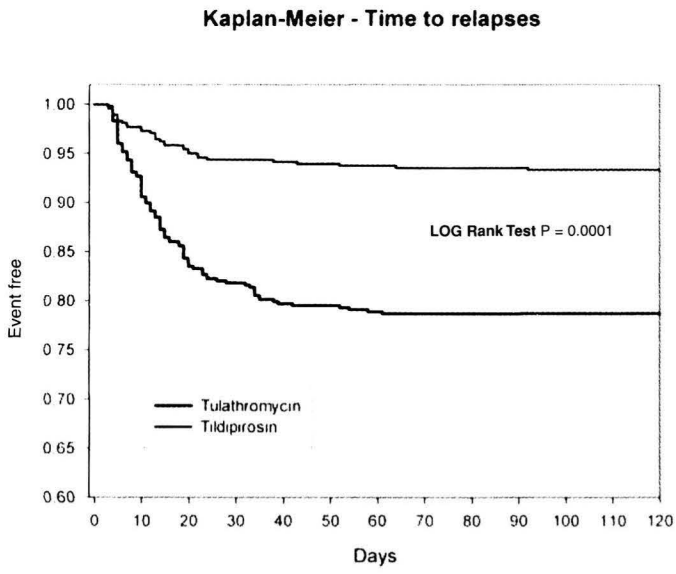

Figure 1. Kaplan-Meier curve of cumulative BRD morbidity (first episode) by days-on-feed for heifers treated with either tulathromycin or tildipirosin at arrival processing.

severity of lesions (Table 4). However, the total number of lungs with lesions was greater than the number (first pulls) of heifers treated (total lung lesions = 24.7%; total BRD initial pulls = 13.4%). There are 3 possible explanations for the discrepancy between the number of animals treated and the number with lung lesions. First, considering that 84.1% of lung lesions detected at slaughter were not in treated animals, some sick animals may not have been detected during the study. This possibility is consistent with a previous report where more than 70% of illness events were not detected.[15] Secondly, given the high percentage of lung lesions, metaphylaxis may have failed to prevent lung lesion development during the arrival period. Finally, there were no acute lung lesions, but rather many minor chronic lesions frequently found in association with pleuritis. Histological examination of the lung samples revealed severe chronic, necrotic bronchopneumonia associated with vasculitis and atelectic areas, confirming the inflammatory nature of the lesions. These findings could be the result of BRD cases that developed and then clinically resolved before arrival at the feedyard.[12] To support this, the Kaplan-

Table 3. Morbidity and daily gain of feedlot heifers fed in facilities with either straw bedding or slatted floors.

Variable	Experimental group		Difference (95 % CI)	*P*-value
	Tulathromycin*	Tildipirosin†		
Straw bedding, N	203	194		
BRD first pull % (N)	18.2 (37)	6.7 (13)	11.5 (2.9÷19.1)	0.0133
ADG‡ (lb)				
Mean ± SD	2.45 ± 0.51	2.62 ± 0.75	-0.18 (-0.31, -0.04)	0.0079
Median (min - max)	2.45 (0.24 – 4.34)	2.60 (-0.15 – 9.74)		
Slatted floor, N	184	204		
BRD first pull % (N)	23.9 (44)	6.8 (14)	17.1 (7.6÷26.7)	0.0005
ADG‡ (lb)				
Mean ± SD	2.23 ± 0.53	2.38 ± 0.51	-0.15 (-0.24, -0.04)	0.0049
Median (min - max)	2.25 (0.26 – 4.10)	2.36 (0.86 – 4.43)		

*Draxxin®, Pfizer Italia srl
†Zuprevo®, MSD Italia srl
‡ADG = average daily gain

Meier curves (Figure 1) showed that observed pathological events were concentrated in the first 30 days after arrival. Nearly 70.7% of first-pulled animals did not have lung lesions at slaughter; therefore, metaphylaxis supplemented by effective therapeutic treatment was an effective strategy under the conditions of this study.

Conclusions

Under the conditions of this study of high-risk heifers, treatment at arrival with tildipirosin reduced morbidity compared to treatment with tulathromycin. Lower BRD morbidity favorably influenced ADG. Health history before arrival at the feedyard is an essential element of information for accurate BRD risk assessment of beef cattle, and may help to evaluate when lung lesions found at harvest may have developed.

Endnotes

[a]Ivomec®, Merial Italia spa
[b]Cattle Master 4®, Pfizer Italia srl
[c]Zuprevo®, MSD Italia srl
[d]Draxxin®, Pfizer Italia srl
[e]Nuflor®, MSD Italia srl
[f]The SAS system release 9.3, 2002-2010. SAS Institute Inc. Cary, NC

Acknowledgements

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Table 4. Carcass traits and lung lesion scores for a subset of feedlot heifers treated with either tulathromycin (n = 226) or tildipirosin (n = 207) at arrival processing.

Variable	Experimental group		Difference (95 % CI)	*P*-value
	Tulathromycin†	Tildipirosin‡		
CCW*				
Mean ± SD	293.91 ± 27.11	298.6 ± 24.83	-4.7 (-9.62, 0.23)	0.0615
Median (min - max)	292 (216 - 386)	294 (232 - 378)		
Dressing percentage				
Mean ± SD	56.98 ± 0.49	56.99 ± 0.51	-0.02 (-0.11, 0.08)	0.7536
Median (min - max)	57 (55.76 - 58.82)	57 (55.65 - 58.72)		
BRD first pull % (N)	19.9 (45)	6.3 (13)	13.6 (7.5÷19.8)	<.0001
Lung lesions location % (N)				
Left cranial lobe	5.3 (12)	8.2 (17)	-2.9 (-7.6÷1.8)	0.22742
Left caudal lobe	2.2 (5)	3.4 (7)	-1.2 (-4.3÷2)	0.45906
Right cranial lobe	16.9 (38)	23.7 (49)	-6.8 (-14.4÷0.8)	0.07907
Right middle lobe	6.7 (15)	5.3 (11)	1.4 (-3.1÷5.8)	0.55482
Right caudal lobe	4.9 (11)	2.9 (6)	2 (-1.6÷5.6)	0.29205
Accessory lobe	0.4 (1)	0.5 (1)	0 (-1.3÷1.2)	0.95286
Total lung	22.1 (50)	27.5 (57)	-5.4 (-13.6÷2.7)	0.19214
N of first pull without lesions (% of first pull)	34 (75.5)	7 (55.8)	ND	
N of lesions without first pull (% of total lung lesions)	39 (78)	51 (89.5)	ND	
Lung score				
Mean ± SD	0.38 ± 0.87	0.44 ± 0.92	-0.06 (-0.23, 0.11)	0.4604
Median (min - max)	0 (0 - 5)	0 (0 - 5)		
Lung score by location % (N)				
0	77.9 (176)	72.5 (150)	ND	
1	13.3 (30)	19.8 (41)	ND	
2	4.9 (11)	2.4 (5)	ND	
3	2.7 (6)	2.9 (6)	ND	
4	0 (0)	1.4 (3)	ND	
5	1.3 (3)	1 (2)	ND	
Pleuritis	13.7 (31)	9.7 (20)	4.1 (-2÷10.1)	0.19103

*CCW = cold carcass weight
†Draxxin®, Pfizer Italia srl
‡Zuprevo®, MSD Italia srl

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