PEER REVIEWED

Effect of Timing of Tilmicosin Metaphylaxis on Control of Bovine Respiratory Disease and Performance in Feeder Cattle

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Abstract

Four-hundred steer and bull calves at high risk of contracting bovine respiratory disease (BRD) were included in a 28-day study to evaluate various tilmicosin metaphylaxis programs for the control of BRD in feeder cattle. The trial animals, which averaged 473 lb at purchase, came from multiple auction markets in the southeast over a 3 day period and were transported to a collection facility in West Point, Mississippi for treatment assignment. Following treatment assignment calves were randomly loaded onto trucks and transported to a research facility in Canyon, Texas. Calves were blocked by day of purchase and randomly assigned to one of four treatments in a randomized complete block design. The four treatments were: 1) non-medicated controls, 2) metaphylactic treatment with tilmicosin at the time of treatment assignment (preshipment treatment), 3) metaphylactic treatment with tilmicosin at the time of processing at the research facility (postshipment treatment), or 4) metaphylactic treatment with tilmicosin at the time of treatment assignment (preshipment) and 72 hours later (postshipment) at the research facility (combination treatment). Tilmicosin was administered at 4.5 mg per lb (10 mg per kg) BW (7.1 ml) based on the average purchase weight. Data were analyzed by analysis of variance using the General Linear Model procedure of SAS. The model included treatment, replication, and treatment x replication as sources of variation.

The BRD morbidity rate was reduced ($P < 0.05$) in all tilmicosin metaphylaxis treatment groups as compared to controls (54, 29, 15, and 15% for treatments 1 through 4, respectively). Furthermore, BRD morbidity was reduced ($P < 0.05$) in the postshipment and combination treatment groups compared to the preshipment treatment group.

All calves experiencing clinical BRD during the trial were treated with tilmicosin at 4.5 mg per lb (10 mg per kg) BW, by subcutaneous (SC) injection. There was no difference between treatment groups in the treatment success rate for animals treated for BRD with tilmicosin. Bovine respiratory disease mortality was higher ($P < 0.05$) in the combination treatment group compared to the preshipment and postshipment treatment groups (2, 0, 0, and 4% for treatments 1 through 4, respectively).

There was no difference in average daily gain (ADG), dry matter intake, or feed/gain among any of the treatment groups during the 28-day study.

Results from this study confirm that metaphylactic use of tilmicosin is an effective tool to control BRD in feeder cattle. Tilmicosin administered at the time of arrival processing (postshipment) was superior to preshipment treatment. Combination treatment (both pre- and postshipment) with tilmicosin did not further decrease BRD morbidity when compared to postshipment treatment alone.

Introduction

Tilmicosin phosphate[a] has been shown to be effective in controlling undifferentiated bovine respiratory disease (BRD) when used in a metaphylaxis program in high-risk cattle.[1,2,5-12,14,17,22] The most appropriate timing of antimicrobial metaphylaxis to minimize BRD morbidity and mortality, reduce animal stress, improve efficiency of animal handling, and maximize performance remains a common question. The factors that influence the risk for severe respiratory disease in calves differ significantly between groups, and as a consequence impact epidemiological factors such as onset of the disease. Predicting the onset of respiratory disease in

calves at high risk of developing BRD can be difficult and thus makes selection of the most appropriate timing for antimicrobial metaphylaxis a difficult decision. Improvement in animal performance following antimicrobial metaphylaxis is likely associated with reduced BRD morbidity.[2,10,17,18,22]

Schumann et al.[18] demonstrated that tilmicosin metaphylaxis reduced ($P < 0.05$) BRD morbidity, improved ($P < 0.01$) average daily gain (ADG), and improved feed efficiency during a 60 day trial period when tilmicosin was administered to animals either on-arrival or three days following arrival (Table 1). No differences in morbidity, feed efficacy or ADG were noted between on-arrival or delayed metaphylaxis. In this trial BRD morbidity was 20% in the control group, which was less than anticipated in high-risk calves.

Duff et al.[3,4] conducted two trials evaluating the efficacy of tilmicosin metaphylaxis for the control of BRD. They administered tilmicosin to auction origin calves either prior to shipment (preshipment) or on-arrival at the feeding facility (postshipment). In both trials, tilmicosin metaphylaxis, either preshipment or postshipment, significantly reduced ($P < 0.05$) BRD morbidity compared to no metaphylaxis. In the first trial[3] there was no difference in pre- vs. postshipment treatment in controlling BRD morbidity, however in the second trial[4] postshipment treatment with tilmicosin reduced ($P < 0.05$) BRD morbidity compared to preshipment treatment. Animal performance, as measured by ADG, did not differ among groups (Table 2).

The objective of this study was to compare the effects of tilmicosin metaphylaxis on the health and performance of high-risk calves treated at different times relative to shipment.

Materials and Methods

Experimental design

Four-hundred steer and bull calves at high risk of contracting BRD were used in the study. The calves were purchased over a three-day period from multiple southeastern US auction markets and held at a collection facility in West Point, Mississippi. Average purchase weight was 473 lb. Fifty-three percent of the calves were bulls. During the morning of the day of shipment, all calves were uniquely identified by numbered ear tags and allocated to one of four treatment groups using a randomization table[15] as they passed through the processing chute. The four treatment groups were: 1) non-medicated control, 2) preshipment tilmicosin metaphylaxis (within 10 hours of shipment), 3) postshipment tilmicosin metaphylaxis (at the time of arrival processing), or 4) combination, preshipment metaphylaxis followed by postshipment metaphylaxis 72 hours later. Calves were blocked by day of purchase (Monday through Wednesday) at the collection facility. Calves were evenly distributed by day of purchase across treatment groups with 160, 110, and 130 arriving at the collection facility three, two, and one day(s) prior to the day of shipment (Thursday), respectively. No attempt was made to block animals based on gender but at completion of treatment assignment bull calves were evenly distributed across all treatment groups.

Table 1. Effect of timing of tilmicosin metaphylaxis on BRD morbidity and performance in feedlot calves (Schumann, et al.)[18]

Item	Control	On-arrival Treatment	Day 3 Treatment
No. animals	103	102	103
Morbidity %	20.0[a]	2.0[b]	1.0[b]
ADG (lb)	2.24[c]	2.64[d]	2.64[d]
Feed/Gain (60 da) (as fed basis)	13.9[c]	12.4[d]	11.8[d]

[ab] Means within rows differ ($P < 0.05$)
[cd] Means within rows differ ($P < 0.01$)

Table 2. Effect of preshipment and postshipment tilmicosin metaphylaxis on BRD morbidity and performance (Duff, et al.)[3,4]

Item	Control	Preshipment	Postshipment
Trial 1 (35 days)			
No. animals	32	31	32
Morbidity %	71.9[a]	45.2[b]	46.9[b]
ADG (lb)	2.60	2.73	2.79
Trial 2 (28 days)			
No. animals	80	80	80
Morbidity %	40.0[a]	18.7[b]	7.5[c]
ADG (lb)	2.94	3.14	2.95

[abc] Means within rows differ ($P < 0.05$)

Rectal temperature of all calves was recorded at the time of treatment assignment. Calves in Groups 2 and 4 were administered tilmicosin subcutaneously (SC) at 4.5 mg per lb (10 mg per kg, 7.1 ml) BW in the shoulder area. Dosage was based on average purchase weight. No signs of BRD were noted at the collection facility, therefore no calves were treated as clinical cases.

Following treatment allocation, all calves were randomly loaded into trucks and shipped to a commercial research facility in Canyon, Texas, arriving approxi-

mately 14 hours later. Calves were offered hay and water upon arrival. All calves were processed six to 15 hours after arrival. Processing included a combination IBR, BVD, PI3, and BRSV vaccine,[b] a clostridial bacterin[c], and an external and internal parasiticide[d]. Bull calves were castrated by application of an elastrator band. Rectal temperature and arrival body weight were collected and recorded for all calves. Calves in treatment Group 3 were given tilmicosin at 4.5 mg per lb (10 mg per kg, 7.1 ml) BW, SC. Calves in treatment Group 4 received their second tilmicosin treatment at 4.5 mg per lb (10 mg per kg, 7.1 ml) BW, SC approximately 72 hours after the first treatment.

Following processing calves were grouped by treatment into pens of 10 calves (10 pens of 10 head per treatment). Pens were 18 ft by 52 ft with fenceline bunk feeding.

On the day following arrival, calves were observed daily for signs of respiratory disease. Calves observed with clinical signs of BRD were assigned a clinical illness score (CIS) of 2 to 5 (Table 3). Calves receiving tilmicosin metaphylaxis (Groups 2, 3, or 4) could not be treated for BRD within 48 hours following tilmicosin administration. Between 48 and 72 hours following tilmicosin metaphylaxis, only calves from these groups with a CIS ≥ 3 could be treated for BRD. Otherwise all calves with a CIS ≥ 2 and rectal temperature ≥ 104.0° F or a CIS ≥ 3 were treated for BRD.

Table 3. Clinical illness scoring

CIS	Description	Clinical appearance
1	Normal	No abnormal signs.
2	Slightly ill	Mildly abnormal character of respiration. Slight depression and gauntness. Possible nasal and/or ocular discharges. Hair coat may be rough.
3	Moderately ill	Moderately abnormal character of respiration. Some dyspnea, depression, gauntness, and nasal and/or ocular discharges. Hair coat may be rough.
4	Severely ill	Severely abnormal character of respiration. Pronounced dyspnea, depression, and gauntness. Nasal and/or ocular discharges. Hair coat may be rough.
5	Moribund	Down, open-mouth breathing, near death.

The supervising veterinarian responsible for observing for signs of BRD and assigning CIS was present during on-arrival processing, including administration of tilmicosin to Group 3 and retreatment of Group 4, therefore was not blinded to the treatment groups.

Calves diagnosed with BRD were weighed and administered tilmicosin at 4.5 mg per lb (10 mg/kg) BW, SC and returned to their trial pen. Calves diagnosed with BRD and treated were observed daily for response to treatment. Treatment response was evaluated based on guidelines described in Table 4. Second line therapy was ceftiofur sodium[e] administered at 1.0 mg per lb (2.2 mg per kg) BW, intramuscularly for three days. A necropsy was performed on all calves that died during the study.

Table 4. Therapy response categories

Therapy response variable	Description
Treatment success	Fully recovered at 72 hours following BRD antibiotic therapy and no additional therapy required in less than 21 days.
Treatment failure	At 72 hours post-BRD antibiotic therapy, clinical illness score (CIS) is greater than time 0 or CIS ≥ 2 and rectal temperature ≥ 104.0° F.
Relapse	An animal that is deemed recovered at 72 hours post-BRD antibiotic therapy, but has another BRD episode ≤ 21 days of the initial therapy regimen and follow-up therapy is required.
New episode	An animal that contracts BRD and requires treatment > 21 days following the initial therapy period.

Calves were fed a ration consisting of steam flaked corn (46.5%), alfalfa hay (23.0%), cottonseed hulls (15.0%), cottonseed meal (4.5%), cane molasses (5.0%), supplement (5.0%) and micro-ingredients (1.0%). This ration was fed twice daily. The amount of feed offered was recorded daily for each pen. Feed weigh-backs were measured and recorded on Trial Days 7 and 28. A final body weight was taken and recorded on Trial Day 28.

Statistical analysis

Data were analyzed by analysis of variance using the General Linear Model procedure of SAS.[16] The model included treatment, replication, and treatment x replication as sources of variation. Prior to the analysis of variance, the pen proportions for morbidity, mortality, treatment success rate, and treatment failure/relapse rate were re-expressed with the arcsine transformation typically used to stabilize the variance of proportions.

Specifically, the transformation was the arcsine of the square root of the observed proportion in each pen. Because the number of animals included in the analysis of the treatment success and the treatment failure/relapse rates differed among pens, a weighted analysis was used to test for differences among treatment groups.

Results

Results of the trial are presented in Tables 5, 6 and 7. One calf was removed from the postshipment group (preexisting severe lameness) and one was removed from the combination treatment group (fractured leg at processing) at the beginning of the trial.

BRD morbidity (Table 5) was reduced ($P < 0.05$) in all tilmicosin metaphylaxis treatment groups as compared to controls (54, 29, 15, and 15% for the control, preshipment, postshipment, and combination treatment groups, respectively). Furthermore, BRD morbidity was reduced ($P < 0.05$) in the postshipment and combination treatment groups as compared to the preshipment treatment group. Although the protocol allowed for calves to be pulled and treated between 48 and 72 hours following metaphylaxis if the CIS was ≥ 3, no calves met this criterion.

Days to first BRD episode were lower in the control group as compared to calves receiving antimicrobial metaphylaxis (3.5, 10.3, 15.3, and 14.9 days for the control, preshipment, postshipment, and combination groups, respectively). Days to first BRD episode were also lower in the preshipment group as compared to the postshipment and combined treatment groups (Table 5).

BRD morbidity rates (Table 6) across treatment groups based on day of arrival at the collection facility were similar to the overall morbidity rates (Table 5). Furthermore, morbidity rates within treatment groups were similar across days of purchase, with the exception of calves purchased on Monday. On this day, the combination treatment group had a morbidity rate of 5.0% as compared to morbidity rates of 23.1 and 18.2% for calves purchased on Tuesday and Wednesday, respectively (Table 6).

The treatment success rate for calves treated individually for BRD with tilmicosin was similar across treatment groups, although there was a trend toward lowered treatment success in calves in the combination group (Table 5). Similarly, the failure/relapse rate for animals treated for BRD was not different across treatment groups. The lack of ability to detect statistical differences among these parameters was not surprising due to the small number of calves developing BRD following tilmicosin metaphylaxis. Even with the treatment failure and relapse rates combined there was inadequate statistical power to detect differences.

There were 2, 0, 0, and 4 BRD related deaths in the control, preshipment, postshipment, and combination treatment groups, respectively. BRD was confirmed upon postmortem examination of all six calves. Three calves' lungs cultured positive for *Pasteurella hemolytica*; one cultured negative; one was not sampled; and one had lung and heart lesions suggestive of a Haemophilus infection, but the cultures were contaminated. BRD mortality was higher ($P < 0.05$) in the combination group as compared to the preshipment and postshipment

Table 5. Effect of timing of tilmicosin metaphylaxis on incidence of BRD

Item	Control	Preshipment	Postshipment	Combination[1]
No. animals/pens	100/10	100/10	99*/10	99**/10
BRD morbidity (%)	54[a]	29[b]	15[c]	15[c] ***
Mean days to first BRD episode	3.5[a]	10.3[b]	15.3[c]	14.9[c]
Treat success (%)	41 (75.9)	24 (82.8)	12 (80.0)	8 (57.1) ***
Treat failure/relapse (%)	13 (24.1)	5 (17.2)	3 (20.0)	6 (42.9) ***
BRD mortality (%)	2[ab]	0[a]	0[a]	4[b]
Mean days to fatal BRD onset	2	—	—	14
Mean preship temp. F°	102.8	102.9	102.7	102.9
Mean postship temp. F°	103.6	103.0	103.6	103.0

[1] Combination metaphylaxis administered preshipment and 72 hours later (postshipment)
* One calf removed with severe lameness at initiation of study
** One calf removed due to fractured leg at initiation of study
*** One BRD mortality occurred acutely, prior to BRD therapy and is not included in treatment success and treatment failure/relapse calculations
[abc] Means within rows differ ($P < 0.05$)

Table 6. Effect of delayed processing and timing of tilmicosin metaphylaxis on BRD morbidity

Item	Control	Preshipment	Postshipment	Combination[1]
3 Days (Monday)				
No. animals	40	40	40	40
Morbidity (%)	19 (47.5)[a]	12 (30.0)[ab]	6 (15.2)[bc]	2 (5.0)[c]
2 Days (Tuesday)				
No. animals	28	28	27	26**
Morbidity (%)	16 (57.1)[a]	9 (32.1)[ab]	4 (14.8)[b]	6 (23.1)[b]
1 Day (Wednesday)				
No. animals	32	32	32*	33
Morbidity (%)	19 (59.4)[a]	9 (25.0)[ab]	5 (15.2)[b]	6 (18.2)[b]

[1] Combination metaphylaxis administered preshipment and 72 hours later (postshipment)
* One calf removed with severe lameness at initiation of study
** One calf removed due to fractured leg at initiation of study
[abc] Means within rows differ ($P < 0.05$)

Table 7. Effect of timing of tilmicosin metaphylaxis on performance (deads out basis)

Item	Control	Preshipment	Postshipment	Combination[1]
No. animals/pens	97[x]/10	99[y]/10	98[z]/10	94[x]/10
Initial weight (lb)	437.4	448.1	440.2	452.0
28-day weight (lb)	525.8	537.1	534.0	544.7
Weight gain (lb)	88.5	89.0	93.9	92.8
ADG (lb)	3.16	3.18	3.35	3.31
DMI (lb)	11.4	12.3	12.4	12.3
Feed/Gain	3.70	3.98	3.93	3.78

[1] Combination metaphylaxis administered preshipment and 72 hours later (postshipment)
[x] One calf removed from group during study due to lameness/downer (non BRD removal)
[y] One calf removed/died during study due to encephalitis/bloat (non BRD removal)
[z] One calf removed/died during study as a digestive dead (non BRD removal)

groups (Table 5). There was no difference in mortality rates between the control, preshipment, and postshipment groups. Mean days to fatal BRD onset were 2 and 14 for the control and combination treatment groups, respectively. Four calves (one from each treatment group) died or were removed during the trial due to non-BRD conditions (Table 7).

Because this was a small pen study and mortalities can have a profound effect on performance, these data were calculated on a deads-out basis. Nevertheless, there were no differences in ADG, dry matter intake (DMI), or feed/gain between any of the treatment groups (Table 7).

Discussion

Antimicrobial metaphylaxis is defined as treatment given to animals experiencing any level of viral or bacterial disease before clinical signs appear.[19,23] The objectives of an antimicrobial metaphylaxis program to control BRD in high-risk calves are to reduce morbidity and mortality and to improve utilization of facilities and personnel. Lower morbidity rates makes detection of sick animals easier and more manageable, thereby reducing labor requirements. Lower morbidity also reduces the potential for over-crowding of hospital facilities.[19] Furthermore, reduced BRD morbidity has been shown to improve performance in feeder calves.[2,10,17,18,22]

Calves receiving tilmicosin metaphylaxis in this study were intentionally not pulled and treated for BRD within 48 hours of their last metaphylactic treatment. This stipulation was made to be consistent with the tilmicosin label, which recommends a 48-hour delay before reevaluation. Since tilmicosin lung levels remain above the minimum inhibitory concentration of the ma-

jority of *Pasteurella haemolytica* isolates for at least 72 hours,[20,21] it could be argued that BRD therapy was not indicated within 72 hours of treatment. In this study, provision was made to individually treat any of the calves in the metaphylaxis treatment groups if they showed severe signs of BRD (CIS ≥ 3) between 48 and 72 hours following metaphylactic treatment. However, no calves receiving metaphylaxis treatment were observed with a CIS ≥ 3 or required BRD therapy during the 48 to 72 hour post-metaphylaxis period.

The results of this study are in agreement with previous reports[1,2,5-12,14,17,22] which concluded that tilmicosin metaphylaxis is a useful tool for reducing BRD morbidity in high-risk cattle. In this study, metaphylactic treatment with tilmicosin at arrival processing was superior to preshipment treatment. The use of tilmicosin both pre- and postshipment (combination group) did not further decrease BRD morbidity as compared to postshipment treatment alone. Treatment success following individual BRD therapy using tilmicosin was not different between treatment groups, which is consistent with other studies[13,22] which suggest that tilmicosin can be successfully used to treat BRD following tilmicosin metaphylaxis. However, it should be noted that due to the small number of animals requiring additional therapy following tilmicosin metaphylaxis, there was little power in the statistical test. To increase the power of the test, either the number of replicates or the number of animals per pen would have to be increased.

The mortality rate was higher in the combination treatment group as compared to either the pre- or postshipment treatment groups. The higher BRD mortality rate in the combination treatment group was unexpected, and likely not repeatable. The only difference in the management of this group compared to the other two treated groups was the additional handling to administer the second metaphylaxis treatment. Because the combination group had the lowest BRD morbidity rate, the extra handling apparently did not increase the amount of stress on these calves. Also, mean days to fatal BRD onset for the combination treatment group was later (14 days) than controls (2 days).

Surprisingly, there was no relationship between BRD morbidity and purchase date or time spent at the collection facility. Furthermore, the metaphylaxis programs used did not appear to affect BRD morbidity differently in animals purchased on various days of the study. It was hypothesized that the BRD morbidity rate would be higher in animals received early in the week (Monday) as compared to later in the week (Wednesday), and that pre-shipment metaphylaxis would be of greatest value when used in calves bought several days before the shipping date, but this was not the case.

In this study there was a numerical increase in ADG in the postshipment and combination treatment groups as compared to the control and preshipment treatment groups, but the differences were not significant. Other studies have shown improvements in animal performance following metaphylaxis, presumably due to the reduction of BRD morbidity.[2,10,17,18,22] A difference in daily gain between the control and treated groups was anticipated. However, approximately 34 replications would have been required in this study to detect a 5% difference in animal performance given the relatively large variation in pen means for average daily gain (3.25 ± 0.24 lb/day).

Results of this study suggest that tilmicosin metaphylaxis treatment at arrival processing is superior to preshipment metaphylaxis. Perhaps under some circumstances preshipment metaphylaxis would be more practical than on-arrival metaphylaxis. If, for example, the handling facility at the receiving location is inadequate to efficiently and safely handle calves, such as calves being turned directly onto pasture, it may be preferable to administer tilmicosin metaphylaxis prior to shipment.

Appropriate timing of postshipment metaphylaxis may be dependent on the morbidity pattern of BRD cases. Tilmicosin metaphylaxis at the time of arrival would likely be superior to delayed metaphylaxis in multiple-source, high-risk calves that often develop BRD soon after shipment. If a majority of the BRD cases occur several days postshipment, delayed metaphylaxis may be indicated.

Conclusion

This study reaffirms the value of antimicrobial metaphylaxis to control BRD in high-risk calves. While all metaphylactic treatments reduced the BRD morbidity rate, on-arrival metaphylaxis was superior to preshipment metaphylaxis in this study. Treatment of calves both preshipment and 72 hours later (postshipment) did not further reduce BRD morbidity rates compared to on-arrival metaphylaxis alone, and certainly was more costly. Many variables affect the appropriate timing of antimicrobial metaphylaxis. Additional work is needed to address appropriate timing of metaphylaxis in situations where morbidity patterns differ significantly from those of most high-risk calves. This study suggests that the most appropriate time for administration of antimicrobial metaphylaxis is at the time of on-arrival processing.

Footnotes

[a] Micotil®, Elanco Animal Health, Indianapolis, IN
[b] Bovi-K 4®, Pfizer Animal Health, Exton, PA
[c] Covexin®, Mallinckrodt, Veterinary Inc., Mundelein, IL
[d] Dectomax®, Pfizer Animal Health, Exton, PA
[e] Naxcel®, Pharmacia & Upjohn, Kalamazoo, MI

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