Tilmicosin as a single injection treatment for respiratory disease of feedlot cattle

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Abstract

Tilmicosin, a new semi-synthetic macrolide antibiotic, was evaluated in eight field trials as a single subcutaneous injection at dosages of 0 (placebo), 5, 10 and 20 mg/kg for the treatment of naturally occurring respiratory disease in feedlot cattle. Animals for these trials were selected from large groups of recently-shipped feeder cattle at the time clinical signs of respiratory disease and body temperature of 40.6°C or higher were observed. Treated animals were evaluated daily for 10 days and finally at day 28. Each animal was weighed on the first day and again on day 28. Animals that died were necropsied. All treatment dosages were effective in significantly lowering mortality, improving weight gains, lowering body temperature, and reducing the severity of clinical signs when compared to the placebo-treated controls. Body temperature was the only variable with statistically significant differences among the dose levels.

Résumé

Administration de tilmicosine, en une seule injection, pour le traitement de maladies respiratoires chez les bovins au parc d'engraissement

Tilmicosine, un antibiotique macrolide semi-synthétique, fut évalué dans huit essais sur le terrain lors de traitement de maladies respiratoires chez les bovins au parc d'engraissement. Une seule dose était administrée par voie sous-cutanée à des dosages de 0 (placebo), 5, 10 et 20 mg/kg. Les animaux choisis pour ces essais furent sélectionnés à partir de groupes de bovins récemment arrivés, présentant des signes cliniques de maladies respiratoires et dont la température corporelle était égale ou supérieure à 40,6°C. Les animaux traités furent évalués quotidiennement pendant 10 jours puis au 28e jour. Les animaux morts furent autopsiés. Le traitement, à chaque dosage, fut efficace de façon significative à réduire le taux de mortalité, à améliorer le gain de poids, à baisser la température corporelle et à diminuer la sévérité des signes cliniques comparativement au groupe témoin ayant reçu le placebo. La température corporelle fut la seule variante ayant une différence statistique significative entre les dosages utilisés. *(Traduit par Dr Thérèse Lanthier)*

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Introduction

Various estimates of morbidity, mortality, and economic loss due to bovine respiratory disease (BRD) have been published over the last several years (1-2). Morbidity was reported to vary from 5-29% and mortality was about 1%. Losses due to mortality, reductions in gain and feed efficiency, and treatment costs could exceed $250 million per year in the United States alone.

The consistent isolation of *Pasteurella haemolytica* from pneumonic lungs of cattle with shipping fever and the increased understanding of the pathogenesis of *P. haemolytica* in pneumonia have resulted in acceptance of this agent as the most important cause of BRD (3). Certain viruses (especially infectious bovine rhinotracheitis virus), certain mycoplasmas, and possibly other agents have been thought to facilitate the establishment of *P. haemolytica* in the lung by impairment of the functions of alveolar macrophages and other host defenses (4). Evidence that other infectious agents are required for *P. haemolytica* to cause pneumonia, however, is not conclusive (5).

Antibacterials have been used extensively for over 40 years for the treatment of BRD. Treatments utilizing various antibacterials frequently are administered daily for several consecutive days. If response to the first antibacterial is poor, a second antibiotic may be administered for another two to three days. Such a program is labor intensive because of the daily handling, and stressful to the cattle due to the restraint involved. An antibacterial treatment which could be administered as a single injection would offer numerous advantages.

We conducted a study to evaluate single injection dosages of tilmicosin for treatment of naturally occurring BRD in newly arrived feedlot cattle. This study included eight trials, all of which followed the same protocol. Tilmicosin is a new semi-synthetic macrolide antibiotic with *in vitro* and *in vivo* activity against both *P. haemolytica* and *P. multocida* (6,7). Trials were conducted in the USA or Canada. American trials were in Idaho (n = 1), Ohio (n = 1) and Texas (n = 2). Canadian trials were in Ontario (n = 1) and Alberta (n = 3). These trials with nonmedicated and tilmicosin-medicated animals served in part to fulfill the USA and Canadian regulatory requirements for approval of tilmicosin injection.

Materials and methods

1. *Experimental cattle — procedures for the processing and selection of animals*

   All animals selected for use in these trials were from larger groups of cattle which had been purchased in small lots at an assembly point or sale barn and then shipped to the trial site. In all cases the trial

site was several hundred kilometers from the assembly point. The methods of purchasing, assembling, and transporting were intended to simulate the methods used for most cattle entering commercial feedlots in the areas in which the trials were conducted. Upon arrival at the trial site, cattle were processed in the usual manner and held in large group-feeding facilities. The receiving and processing programs varied slightly at each trial site. Cattle were injected with the usual immunizing agents used at feedlots, i.e. infectious bovine rhinotracheitis, parainfluenza-3 virus, bovine virus diarrhea virus, and clostridial vaccines.

In addition, most were treated with ivermectin (Ivomec, MSDAgvet, Division of Merck and Co. Inc., Rahway, New Jersey, USA) for parasites. In two of the four Canadian trials, all cattle received 30 mL of long-acting oxytetracycline (Liquamycin LA200, Pfizer Inc., New York, New York, USA) as part of the receiving health program. Effects due to differences in procedures from one trial to another were accounted for by the location term in the statistical model.

All cattle were observed daily for signs of respiratory disease, including dyspnea, nasal discharge, general condition and alertness, and appetite. Any animal showing such signs was moved to a hospital pen or treatment area where it could be restrained, weighed, and further examined. Only animals with signs of respiratory disease and a body temperature of 40.6°C or higher were used in these trials.

2. *Tilmicosin treatment*

The tilmicosin formulation used in these experiments contained 300 mg tilmicosin activity/mL in a 25% propylene glycol aqueous solution. The identical formulation without tilmicosin was used as the placebo treatment.

Animals meeting the above criteria for signs of respiratory disease and body temperature were assigned to one of four treatments: placebo; tilmicosin, 5 mg/kg body weight; tilmicosin, 10 mg/kg body weight; or tilmicosin, 20 mg/kg body weight. As the animals entered the study, treatments were assigned randomly within groups of four by use of a predetermined randomization schedule. Treatments were coded so as to be blinded to the investigator. The rationale for use of a single injection rather than several daily injections was based upon preliminary data which showed that one injection of tilmicosin resulted in prolonged serum and tissue levels (T. D. Thomson, Lilly Research Laboratories, Greenfield, Indiana, USA). All treatments were administered either subcutaneously in the neck or in the area just caudal to the scapula and approximately 15–25 cm ventral to the midline. This area over the ribs was readily accessible in the working chute. Each animal received only a single injection of placebo or tilmicosin. Animals receiving only the placebo formulation received the dosage volume equivalent to the tilmicosin 10 mg/kg dosage. The number of animals selected for treatment at the eight trial sites varied from 8–12 animals per dosage.

Table 1. Mortality with various tilmicosin treatment regimens

Experiment no.	Dose of tilmicosin (mg/kg)			
	0	5	10	20
1	4/9	1/9	0/9	0/9
2	3/9	0/9	0/8	0/9
3	2/9	0/9	0/9	0/9
4	3/9	0/9	0/9	0/9
5	2/12	2/12	0/12	0/12
6	1/11	0/11	0/10	0/11
7	1/8	0/8	1/8	2/8
8	1/8	0/8	0/8	0/8
Total	17/75[a]	3/75[b]	1/73[b]	2/75[b]

One animal (experiment 2) died of peritonitis,, data excluded
One heifer (experiment 6) aborted calf, day 19, data excluded
[a,b]Ratios without a common superscript are significantly different ($p < 0.05$)

3. *Variables used for detection of respiratory disease and treatment response*

Nasal swabs were collected from each animal on the day the animal was assigned to a treatment group. The body temperature of each animal was recorded daily for the first 10 days, and on day 28. Sheets for recording daily observations of each clinical sign were designed in such a way that the observer was not able to readily ascertain the score given on any previous day, so as to minimize assessment bias.

The body weight of each animal was recorded on the day each animal was treated and at the end of the trial on day 28.

Each animal was evaluated daily for the first 10 days following treatment for the following clinical signs: general condition and alertness; respiratory condition; appetite and fill; nasal discharge; and ocular discharge. The scoring system used for recording the severity of these clinical signs was 0 for normal, 1 for mild, 2 moderate, and 3 for severe. With few exceptions all daily observations within a trial were made by the same person.

Animals that died during the 28-day trial period were necropsied and pulmonary lesions, if present, were scored visually according to the following scale:

0 = no lesions
1 = slight, 1–5% involvement
2 = moderate, 6–20% involvement
3 = severe, >20% involvement

All pneumonic lesions were cultured aerobically at 37°C using 5% ovine trypticase soy agar plates for bacterial respiratory pathogens.

4. *Statistical methods*

Mortality data were analyzed using the categorical data modeling procedure, Catmod, in SAS (8). With this procedure, location effect and location by treatment interaction are tested in addition to treatment contrasts using log-linear models. Weight gain data were analyzed using the general linear model procedure, GLM, in SAS. From this procedure, treatment contrasts and least squares means

Table 2. Least squares means of weight gains and average daily temperatures (°C)

	Dose of tilmicosin (mg/kg)			
Days	**0**	**5**	**10**	**20**
28-day gain, kg	14.31[a]	31.48[b]	33.54[b]	33.80[b]
1–10 days mean temp	40.0[a]	39.5[b]	39.4[bc]	39.2[c]

[abc]Values in horizontal rows without a common superscript are significantly different ($p < 0.05$)

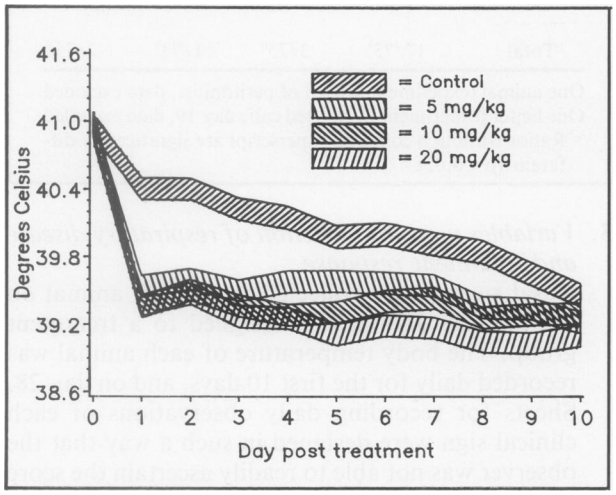

Figure 1. Mean daily rectal temperature ± 1 SD beginning on the day of tilmicosin treatment.

were obtained. The model for this analysis included adjustment for location and for location by treatment interaction. Daily temperatures and clinical signs were analyzed with the GLM procedure using a model similar to the model used for weight gain, but one in which the day effect was modeled as repeated measures. There was a small amount of imbalance due to deaths in the nontreated groups, but the amount of imbalance did not have a consequential effect. Values on day 0 for temperature and clinical scores were initially used as covariates but were found to be nonsignificant and had no effect on the outcome; thus, they were eliminated from the model.

Results

Case-specific mortalities in the nonmedicated cattle were 17/75 (22.7%) compared to 3/75 (4%) in the tilmicosin-medicated group (5 mg/kg) with the highest number of deaths (Table 1). All three tilmicosin dosages significantly ($p < 0.05$) reduced mortality over that of the controls (placebo). There were no significant differences in mortality among the tilmicosin levels.

Cattle in the USA trials had an initial mean weight of 187 kg (range 179–197 kg) while cattle in the Canadian trials had a mean weight of 282 kg (range of 267–291 kg). Gain for all tilmicosin-medicated groups was greater than twice that of the nonmedicated calves (Table 2). All three tilmicosin dosages resulted in significantly ($p < 0.05$) improved weight gains over the controls, but again there was no difference among tilmicosin levels.

All tilmicosin doses resulted in a significant ($p < 0.05$), marked decrease in body temperature within 24 hours following treatment (Figure 1). Each of the three dosages of tilmicosin was effective in reducing the temperature as compared to the controls for the first 10 days following injection. Only the difference between the 5 mg/kg dose and the 20 mg/kg dose was significant ($p < 0.005$) (Table 2). Significantly ($p < 0.05$) lower scores for each clinical sign were found for each tilmicosin-treated group when compared to the respective score for the nonmedicated cattle. There was no significant difference among the three tilmicosin treatment groups.

Microbiological studies conducted on either the nasal swabs collected at the time the animals were treated or the lung tissue specimens collected at necropsy from those animals which died yielded *P. haemolytica* serotype 1 (determined by Dr. G. Frank, NADL, Ames, Iowa, USA) from animals at all of the trial sites. *Haemophilus somnus* was isolated from two animals in one trial; otherwise, no other bacterial pathogens were isolated.

Discussion

These initial field trials with tilmicosin administered as a single injection for the treatment of BRD in feedlot cattle confirmed the effectiveness reported earlier of tilmicosin in trials with neonatal calves (9). In those trials, single injections of 10, 20 and 30 mg/kg of tilmicosin were evaluated, and 20 mg/kg was determined to be the optimal dose. It was considered probable that the disease in feedlot cattle would be less severe and that the optimal dosage of tilmicosin for treatment of BRD in feedlot cattle would be lower than that needed in neonatal calves. Therefore, dosages were reduced to 5, 10 and 20 mg/kg in the trials reported herein. Levels of 5, 10 and 20 mg/kg were effective in preventing mortality, reducing body temperatures, and improving weight gain. A clinically important variable that gave a dose-dependent response was body temperature, where 20 mg/kg resulted in significantly lower temperatures than 5 mg/kg. The 10 mg/kg level resulted in an average temperature between the means for the 5 and 20 mg/kg treatments. This result suggests that, with more severe infections, a level higher than 5 mg/kg would be needed for maximal effectiveness.

If upon wide usage tilmicosin proves to be as effective as shown in these initial field trials, the single injection

and low volume will provide significant improvements in the medication of feedlot cattle with BRD. Cattle will benefit from reduced stress, pain, and tissue irritation. There could also be significant reductions in the labor and costs involved because a single injection of tilmicosin could allow for the animal to be left in its home pen. Some recent trials conducted in Canada (10), in which tilmicosin at 10 mg/kg was compared to currently approved injectable antibiotics for treatment of BRD, indicate that this method of management may be feasible. In those trials, tilmicosin and long-acting oxytetracycline as single injections were compared to multi-day ceftiofur, trimethoprim/sulfadoxine, and oxytetracycline LP treatments. Tilmicosin was equally or more effective than the other antibacterials. Tilmicosin has also been used prophylactically on the day calves arrived at the feedlot (11); it significantly reduced treatment rate and improved gain and feed efficiency over nonmedicated controls. CVJ

References

1. Martin SW, Meek AH, Davis DG, Johnson JA, Curtis RA. Factors associated with mortality and treatment costs in feedlot calves. The Bruce County beef project, years 1978, 1979, 1980. Can J Comp Med 1982; 46: 341–349.
2. Frank GR, Salman MD, MacVean DW. Use of a disease reporting system in a large beef feedlot. J Am Vet Med Assoc 1988; 192: 1063–1067.
3. Frank GH. The role of *Pasteurella haemolytica* in the bovine respiratory disease complex. Vet Med 1986; (Sept): 838–846.
4. Wilkie PE, Shewen PA. Defining the role that *Pasteurella haemolytica* plays in shipping fever. Vet Med 1988; (Oct): 1053–1058.
5. Shewen PE. *Pasteurella*. In: Gyles C, Thoen CO, eds. Pathogenesis of Bacterial Infections in Animals. 1st ed. Ames, Iowa: Iowa State University Press, 1986: 150.
6. Debono M, Willard KE, Kirst HA, *et al.* Synthesis and antimicrobial evaluation of 20-deoxo-20-[3,5-dimethyl piperidin-1-yl] desmycosin [tilmicosin, EL-870] and related cyclic amino derivatives. J Antibiotics 1989; 42: 1253–1267.
7. Ose, EE. *In vitro* antibacterial properties of EL-870, a new semi-synthetic macrolide antibiotic. J Antibiotics 1987; 40: 190–194.
8. SAS. SAS User's Guide: Statistics. Cary, North Carolina: SAS Institute Inc., 1985.
9. Ose EE, Tonkinson LV. Single dose treatment of neonatal calf pneumonia with the new macrolide antibiotic, tilmicosin. Vet Rec 1988; 123: 367–369.
10. Merrill JK, Tonkinson LV. The effectiveness of micotil for the treatment of bovine respiratory disease. Bovine Practitioner 1989; 24: 26–28.
11. Schumann FJ, Janzen ED, McKinnon JJ. Prophylactic tilmicosin medication of feedlot calves at arrival. Can Vet J 1990; 31: 285–288.