ARTICLES

A comparison of trimethoprim-sulfadoxine and ceftiofur sodium for the treatment of respiratory disease in feedlot calves

G. Kee Jim, Calvin W. Booker, P. Timothy Guichon

Abstract

A field trial was performed to compare trimethoprim-sulfadoxine to ceftiofur sodium in the treatment of bovine respiratory disease (BRD) in feedlot calves. Five-hundred-and-fifty-five recently weaned, crossbred beef calves, with naturally occurring cases of BRD, were randomly assigned to either trimethoprim-sulfadoxine or ceftiofur sodium treatment groups. The effectiveness of the antibiotics was assessed by comparing relapse rates, three day treatment response rates, mortality rates, chronicity rates, and wastage rates. There was no statistical difference in the first or second relapse rates between the two groups. For the initial therapy, first relapses, and overall treatment episodes, a significantly greater proportion of the calves treated with ceftiofur sodium responded to three days of therapy than those treated with trimethoprim-sulfadoxine ($p < 0.05$). This resulted in a 10% reduction in treatment costs for calves in the ceftiofur group. There were significantly lower mortality and wastage rates attributable to BRD in the ceftiofur sodium group than in the trimethoprim-sulfadoxine group ($p < 0.05$). However, there were no significant differences in overall mortality, overall chronicity, or overall wastage rates between the treatment groups.

Résumé

Comparaison entre le triméthoprime-sulfadoxine et le ceftiofur de sodium pour le traitement de maladies respiratoires chez les veaux en parc d'engraissement

Une étude sur le terrain a été effectuée pour comparer l'efficacité du triméthoprime-sulfadoxine au ceftiofur de sodium pour le traitement de maladies respiratoires chez les veaux en parc d'engraissement. Cinq cent cinquante-cinq veaux de boucherie, de race croisée, récemment sevrés et présentant des signes de maladies respiratoires acquises de façon naturelle ont été divisés au hasard en deux groupes de sujets. Un groupe a reçu un traitement au triméthoprime-sulfadoxine et l'autre a reçu du ceftiofur de sodium. L'efficacité des antibiotiques a été évaluée en comparant le taux de récidives, le taux de réponse à un traitement d'une durée de trois jours, le taux de mortalité, le caractère de chronicité et le taux de pertes. Il n'y avait pas de différence significative entre les taux de la première ou de la deuxième récidive entre les deux groupes traités. Considérant le traitement initial, les premières récidives et l'ensemble des épisodes de traitement, les données ont démontré qu'une plus grande proportion de veaux traités au ceftiofur de sodium ont répondu de façon significative au traitement d'une durée de trois jours comparativement à ceux traités au triméthoprime-sulfadoxine ($p < 0,05$). Ceci a eu pour effet de réduire les coûts du traitement de 10 % pour les veaux traités au ceftiofur. Les taux de mortalité et de pertes attribuables aux maladies ont été comparativement plus faibles, de façon significative, pour le groupe de veaux traités au ceftiofur ($p < 0,05$). Toutefois, il n'y a pas eu de différence significative entre les deux groupes de traitement concernant l'ensemble des mortalités, la chronicité globale et les taux totaux des pertes.

(Traduit par Dr Thérèse Lanthier)

Can Vet J 1992; 33: 245-250

Introduction

Acute undifferentiated bovine respiratory disease (BRD), or "shipping fever", has been extensively documented as the most economically significant health problem of feedlot cattle (1-5). In western Canada, therapeutic drug expenditures to combat BRD can significantly affect economic returns in calves which experience a high BRD mortality rate. Thus, for the feedlot veterinarian, it is of paramount importance to determine which antimicrobials are the most efficacious for treatment.

Ceftiofur is a semisynthetic antibiotic classified as a third generation cephalosporin. Like the penicillins, ceftiofur inhibits cell wall synthesis in susceptible bac-

Feedlot Health Management Services, Postal Bag Service 5, 7-87 Elizabeth Street, Okotoks, Alberta T0L 1T0 (Jim, Guichon); Department of Herd Medicine and Theriogenology, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0 (Booker).

teria and is considered bactericidal. Moreover, third generation cephalosporins have considerably more activity against gram-negative organisms than first or second generation cephalosporins. In Canada, ceftiofur (Excenel, Upjohn Animal Health, Orangeville, Ontario) was approved for intramuscular use in beef and nonlactating dairy cattle in 1988.

The purpose of the investigation reported herein was to compare the efficacy of a commonly used, commercially available antimicrobial, trimethoprim-sulfadoxine (Trivetrin, Coopers Agropharm Inc., Ajax, Ontario) to a newly available antimicrobial, ceftiofur (Excenel, Upjohn), in the treatment of BRD in a commercial feedlot.

Materials and methods

The trial was conducted in a commercial feedlot near Strathmore, Alberta, which has a capacity of 20,000 head. The animals utilized in the study were recently weaned, crossbred beef steer calves purchased from auction markets throughout western Canada. The calves were approximately 5–10 months of age and weighed between 250 and 350 kg.

Upon arrival at the feedlot, calves were processed in a standard manner and sent to a designated pen within 24 hours. Each calf was ear tagged (to provide unique, individual animal identification), branded, given an injection of vitamins A and D (Poten AD, rogar/STB, Pointe Claire-Dorval, Quebec), treated with ivermectin (Ivomec, MSDAgvet, Kirkland, Quebec), implanted with a progesterone estradiol implant (Steer-oid, Boehringer Ingelheim Animal Health, Burlington, Ontario) and vaccinated against infectious bovine rhinotracheitis (IBR), parainfluenza-3 (PI_3) and *Haemophilus somnus* (IBR-PI_3/Somnugen, Boehringer Ingelheim Animal Health). In addition, the calves received a multivalent clostridial vaccine (Clostri-Bac 8, Coopers Agropharm Inc.).

Routine management

The calves were housed in open air, dirt floor pens arranged side by side with a central feed alley. Each pen measured 55 × 80 m, and there were approximately 300 calves per pen. The calves were fed a ration formulated to the standard nutritional requirements of feedlot cattle. The ration was prepared in a modern milling facility, equipped with overhead bins. The ration was delivered to the pens once or twice daily by trucks equipped with mixers, and water was provided *ad libitum*.

Experimental design

It was anticipated that ceftiofur sodium would decrease the first relapse rate from 40% to 25%. Conditional on at least a 90% chance of detecting a decrease as large as this or larger and a 95% certainty that this difference was not due to chance, approximately 275 animals per treatment group would be required. Including 275 animals per treatment group resulted in a power of approximately 60% to detect a 50% reduction in mortality, chronicity, or wastage rates.

Calves from seven pens, each containing 300–307 animals, which arrived at the feedlot between October 20, 1987, and November 3, 1987, were the candidates for the trial. In this investigation, the case definition for BRD was an elevated rectal temperature ($\geq$ 40.3°C) within three to five days postarrival. Exclusion criteria were calves with a previous treatment history for any disease, obvious clinical signs attributable to organ systems other than the respiratory system, or moribund animals.

At the time of selection, the experimental calves were weighed and randomly assigned to one of two treatments: T/S, which was trimethoprim-sulfadoxine (Trivetrin, Coopers Agropharm Inc.), at the rate of 2.66 mg trimethoprim + 13.33 mg sulfadoxine per kg body weight intramuscularly (IM) once daily for three consecutive days; or Cef, which was ceftiofur sodium (Excenel, Upjohn), at the rate of 1.1 mg per kg body weight IM once daily for three consecutive days. Two-hundred-and-seventy-nine calves were assigned to the T/S group and 276 calves assigned to the Cef group. The calves were housed in a hospital facility during the treatment period.

Following administration of the third injection, calves were returned to the home pen if their body temperature was $\leq$40.3°C. If the body temperature was >40.3°C, the calf was treated with the initial antibiotic, at the same dose, for two additional days. If the body temperature was $\leq$40.3°C following administration of the fifth injection, the calf was returned to the home pen. If the body temperature was >40.3°C, the calf was sent to the chronic pen.

Upon returning to the home pen, the treated calves were observed once to twice daily by experienced pencheckers. The pencheckers were blind to treatment status. Those calves deemed to be "sick" by the pencheckers were taken to the hospital facility. A relapse was defined as an animal with a body temperature of $\geq$40.0°C and was treated in the manner described for initial therapy. Switching of antimicrobials was not permitted, and fifteen individual treatments were the maximum permitted for each animal. The trial calves were followed from the day of first treatment until they were sold for slaughter (approximately 180 days).

Calves in the chronic pen were examined weekly and returned to the home pens as "recovered" based on their rectal temperature (<40.0°C), attitude, and appearance. Calves still in the chronic pen 90 days after the last animal was placed on the trial were defined as "chronics". Chronics were examined by the feedlot veterinarians to determine the most probable cause of illness, and were classified as having either BRD, or being non-BRD cases. All dead calves were necropsied by the attending feedlot veterinarian and tissues were submitted to the Regional Veterinary Diagnostic Laboratory in Airdrie, Alberta, for confirmation of the cause of death.

Analysis of data

Data were organized into 2 × 2 tables facilitating the calculation of three-day treatment response rates for the initial treatment episode, the first relapse, the second relapse, and overall treatment episodes for the

Table 1. Relapse rates of calves treated for bovine respiratory disease with either trimethoprim-sulfadoxine (T/S) or ceftiofur (Cef)

	T/S	Cef
Initial no. of cases	267	263
No. of first relapses	129	128
First relapse rate[a]	48.3	48.7
No. of second relapses	63	48
Second relapse rate[b]	48.8	37.5

[a]Expressed as the percentage of the initial cases that relapsed
[b]Expressed as the percentage of the first relapses that relapsed a second time

trimethoprim-sulfadoxine and ceftiofur groups. In addition, risk rates were calculated for first and second relapses, overall mortality, BRD mortality, overall chronicity, and BRD chronicity for each treatment group. The mortality data and the chronicity data were combined and defined as wastage. All data were then entered into a statistics program (True Epistat, Epistat Services, Richardson, Texas) and chi-square tests of association, without correction for continuity, were used to determine the statistical significance of the differences in rates between the treatment groups (6).

Results

There was no statistical difference in the relapse rates between the two treatment groups (Table 1). The ceftiofur group had a significantly lower percentage of cases that required more than three days of treatment for the initial treatment episode, the first relapse, and overall treatment episodes ($p < 0.05$, Table 2). There was no statistical difference in the overall mortality rates between the treatment groups; however, the BRD mortality rate was significantly lower in the ceftiofur group ($p < 0.05$), (Table 3). There were no statistical differences in the overall proportion of chronics or in the BRD proportion of chronics between the treatment groups. Also, there was no significant difference in the overall wastage rate between the groups. The BRD wastage rate was significantly lower in the ceftiofur group ($p < 0.05$), (Table 3).

The data from 25 calves (12 from the T/S group and 13 from the Cef group) were excluded from the analysis because of treatment protocol errors.

Table 2. Three-day treatment responses[a] of calves treated for bovine respiratory disease with either trimethoprim-sulfadoxine (T/S) or ceftiofur (Cef)

	T/S	Cef
Initial episode	212	240
Response rate[b]	79.4[c]	91.3[c]
First relapses[a]	95	112
Response rate[b]	73.6[d]	87.5[d]
Second relapse[a]	46	41
Response rate[b]	73.0	85.4
Over all treatment episodes[a]	377	424
Response rates[b]	77.1[e]	89.8[e]

[a]Number of treated calves responding to three days of therapy
[b]Response rates are expressed as the percentage of treated calves responding to three days of therapy
[c]Rates are statistically different ($p < 0.001$)
[d]Rates are statistically different ($p < 0.05$)
[e]Rates are statistically different ($p < 0.001$)

Table 3. Mortality, chronicity, and wastage of calves treated for bovine respiratory disease with either trimethoprim-sulfadoxine (T/S) or ceftiofur (Cef)

	T/S	Cef
Overall mortality[a]	19	14
Mortality rate	7.1	5.3
Overall chronicity[a]	11	10
Chronicity rate	4.1	3.8
Overall wastage[a]	30	24
Wastage rate	11.2	9.1
BRD mortality[b]	15	6
BRD mortality rate	5.6[c]	2.3[c]
BRD chronicity[b]	6	2
BRD chronicity rate	2.2	0.8
BRD wastage[b]	21	8
BRD wastage rate	7.9[d]	3.0[d]

[a]Mortality, chronicity, or wastage due to all causes
[b]Those cases of mortality, chronicity, or wastage due to respiratory disease
[c]Rates are statistically different ($p < 0.05$)
[d]Rates are statistically different ($p < 0.05$)

Discussion

In this study, ceftiofur was a superior antimicrobial as compared to trimethoprim-sulfadoxine for the treatment of BRD because the three-day treatment response rate was significantly higher for the ceftiofur group over all episodes of treatment. Assuming that the daily therapy costs were equal for both trimethoprim-sulfadoxine and ceftiofur at $3.00 CDN per day per animal, and utilizing the three-day and the five-day treatment response rates over all treatment episodes for each treatment group, the cost of treatment for the entire trimethoprim-sulfadoxine group was $5,073.00 CDN and the cost of treatment for the ceftiofur group was $4,536.00 CDN. Therefore, the cost of treatment for calves in the ceftiofur group was approximately 10% less than the cost of treatment for calves in the trimethoprim-sulfadoxine group. There were no significant differences in the overall mortality rate or in the overall wastage rate between the two treatment groups; therefore, additional economic benefits could not be attributed to the ceftiofur group.

The average number of treatment days for each treatment group was not calculated because the design

of the trial allowed animals to be treated for either three days or five days. These are categorical data rather than continuous data, and average number of treatment days is not a statistically valid parameter.

Rational selection of an antimicrobial for the treatment of BRD is a difficult task for the feedlot veterinarian. First, the approach of choosing an antimicrobial based on the susceptibility patterns that emerge from pretreatment nasal swabs is not practical under field conditions. In addition, much controversy exists regarding the correlation between culture and sensitivity of pathogens isolated from nasal swabs and the actual pathogen in the lung (7,8). The extent to which sensitivity patterns are biased when pathogens are isolated from only 20–50% of the pretreatment nasal swabs is unknown. Moreover, a recent study demonstrated that sensitivity results obtained from pretreatment nasal swabs using the Kirby-Bauer technique do not correlate with the subsequent clinical response obtained with various antimicrobials (9). Second, it has been demonstrated that therapy with a particular antimicrobial agent increases the resistance level of the primary pathogen to that antimicrobial (10). Therefore, selection of an antimicrobial based on the sensitivity results obtained from culturing lungs of dead cattle is invalid. However, this inappropriate technique has resulted in the tenuous suggestion that treatment failure in cases of BRD is caused by "resistant" *Pasteurella haemolytica* (11). Third, the reliability of antimicrobial susceptibility tests has been criticized to the point of questioning whether they are worth performing under any circumstances (7,8). In summary, the recent literature suggests that clinical microbiological findings and pharmacokinetic considerations do not necessarily correlate with therapeutic outcome. Thus, the definitive evaluation of an antimicrobial in reference to a particular disease should be determined by utilizing spontaneously occurring cases of the disease in a properly designed field trial. Unfortunately, there are only a few BRD therapy trials in the veterinary literature with appropriate experimental design, number of cases, and characterization of response parameters (9,12). Ironically, Hjerpes' work (13), which is now 15 years old and is largely anecdotal evidence regarding the effectiveness of various antimicrobials in the treatment of BRD, is still utilized as a standard reference. However, in our opinion, a consulting veterinarian to a modern feedlot cannot continue to provide simple anecdotal information regarding antimicrobial therapy.

The significance of this paper *per se* is not the results, but rather the methodology utilized to evaluate antimicrobials. Obviously, there will be debate regarding the evaluation techniques employed, particularly with respect to case definition, response variables, and outcome measurements. However, these discussions are necessary to provide impetus for developing improved field trials that result in a more scientific selection of antimicrobials to combat BRD.

Acknowledgments

We thank Dr. Peg Northcote for her assistance in conducting this trial. This project was wholly supported by a research grant from the Upjohn Company — Animal Health, Orangeville, Ontario. CVJ

References

1. Yates WDG. A review of infectious bovine rhinotracheitis, shipping fever pneumonia and viral-bacterial synergism in respiratory disease of cattle. Can J Comp Med 1982; 46: 225–263.
2. Church TL, Radostits OM. A retrospective survey of diseases of feedlot cattle in Alberta. Can Vet J 1981; 22: 27–30.
3. Martin SW, Meek AH, Davis DG, *et al.* Factors associated with mortality in feedlot cattle: the Bruce County beef cattle project. Can J Comp Med 1980; 44: 1–10.
4. Frank GH. *Pasteurella haemolytica* and respiratory disease in cattle. Proc Annu Meet US Anim Health Assoc 1979; 83: 153–160.
5. Jensen R, Pierson RE, Braddy PM, *et al.* Shipping fever pneumonia in yearling feedlot cattle. J Am Vet Med Assoc 1976; 169: 500–506.
6. Steel RGD, Torrie JH. Principles and Procedures of Statistics: A Biometrical Approach. New York: McGraw Hill Book Co., 1980: 502.
7. Greenwood D. In vitro veritas? Antimicrobial sensitivity tests and their clinical relevance. J Infect Dis 1981; 144: 380–385.
8. Woolcock JB, Mutimer MD. Antibiotic susceptibility testing: caeci caecos ducentes? Vet Rec 1983; 113: 125–128.
9. Mechor GD, Jim GK, Janzen ED. Comparison of penicillin, oxytetracycline and trimethoprim-sulfadoxine in the treatment of acute undifferentiated bovine respiratory disease. Can Vet J 1988; 29: 438–443.
10. Martin SW, Meek AH, Curtis RA. Antimicrobial use in feedlot calves: Its association with culture rates and antimicrobial susceptibility. Can J Comp Med 1983; 47: 6–10.
11. Fales WH, Selby LA, Webber J, *et al.* Resistance among *Pasteurella* spp. recovered from Missouri and Iowa cattle with bovine respiratory disease complex. J Am Vet Med Assoc 1982; 181: 477–479.
12. Bateman KG, Martin SW, Shewen P, Menzies PI. An evaluation of antimicrobial therapy for undifferentiated bovine respiratory disease. Can Vet J 1990; 31: 689–696.
13. Hjerpe CA. Clinical management of respiratory disease in feedlot cattle. Vet Clin North Am (Large Anim Pract) 1983; 5: 119–142.

Correction/Correction d'auteur

Compendium of animal rabies vaccines marketed in Canada

Répertoire des vaccins antirabiques pour animaux vendus au Canada

Can Vet J 1992; 33: 101–104

For the product IMRAB, manufactured by Rhône Mérieux in the species ferrets, the recommended revaccination should be **12 months and not 36 months.**

Agriculture Canada apologizes for this inadvertent error.

Dans la description du produit IMRAB fabriqué par Rhône Mérieux, pour les furets, la recommandation pour la rappel du vaccin aurait dû se lire **12 mois et non pas 36 mois.**

Le ministère canadien de l'Agriculture offre ses excuses pour cette erreur malheureuse.