A comparison of the clinical field efficacy and safety of florfenicol and tilmicosin for the treatment of undifferentiated bovine respiratory disease of cattle in western Canada


Abstract — We compared the field efficacy of a new antibiotic, florfenicol, with tilmicosin in the treatment of naturally occurring undifferentiated bovine respiratory disease. Beef calves with rectal temperatures greater than 40.5°C and signs compatible with undifferentiated bovine respiratory disease were entered into the trial. Calves were randomly assigned to receive either florfenicol (20 mg/kg bodyweight intramuscularly; 2 injections 48 h apart) or tilmicosin (10 mg/kg bodyweight subcutaneously; 1 injection). Clinical measures of efficacy included mortality, rectal temperature, illness index score, assessment of treatment success or failure, and the number of relapses or reinfections. Performance was assessed based on weight gains from day 0 to day 90. Two hundred and twenty calves entered the trial; 112 received florfenicol and 108 received tilmicosin. Seventeen deaths occurred between day 0 and day 90, but only 10 during the 28-day trial period. Seven calves receiving tilmicosin died, compared with 3 receiving florfenicol ($P = 0.20$). Of the 220 initial treatments, 45 (20%) were categorized as treatment failures; 27 in the tilmicosin group and 18 in the florfenicol group ($P = 0.10$). The number of calves experiencing a 2nd relapse was significantly different, with 17 of 30 (57%) calves on tilmicosin compared with 7 of 26 (27%) calves on florfenicol relapsing at least twice ($P = 0.02$). Average daily gains over 90 days were 1.55 kg/day for florfenicol-treated calves and 1.51 kg/day for tilmicosin-treated calves. No significant adverse reactions were noticed with either drug. Results indicate that florfenicol and tilmicosin are comparable in the treatment of undifferentiated bovine respiratory disease in western Canada.

Résumé — Comparaison de l’efficacité clinique et de l’innocuité du florfénicol et de la tilmicosine dans le traitement du complexe respiratoire bovin dans l’Ouest canadien. Nous avons comparé l’efficacité clinique d’un nouvel antibiotique, le florfénicol, et la tilmicosine dans le traitement du complexe respiratoire bovin survenant de façon naturelle. Des veaux de boucherie qui présentent une température rectale supérieure à 40,5 °C et des signes compatibles avec le complexe respiratoire bovin ont été retenus pour cette épreuve. Les veaux ont été assignés au hasard au traitement au florfénicol (20 mg par kg de poids corporel, intramusculaire; 2 injections à 48 h d’intervalle) ou à la tilmicosine (10 mg par kg au poids corporel, sous-cutané; 1 injection). Les mesures cliniques d’efficacité comprenaient la mortalité, la température rectale, le classement à l’index de maladie, le classement du traitement en succès ou en échec et le nombre de rechutes ou de réinfections. La performance était évaluée sur les gains de poids du jour 0 au jour 90. Deux cent vingt veaux ont fait partie de l’épreuve; 112 ont reçu le florfénicol et 108 la tilmicosine. Dix-sept mortalités sont survenues entre les jours 0 et 90 mais seulement 10 au cours de 28 jours de l’épreuve. Sept veaux traités à la tilmicosine sont morts comparés aux 3 traités au florfénicol ($P = 0.20$). Sur les 220 animaux soumis à l’épreuve, 45 (20%) des traitements ont été considérés comme des échecs; 27 dans le groupe de la tilmicosine et 18 dans celui du florfénicol ($P = 0.10$). Le nombre de veaux ayant eu au moins une rechute était significativement différent, 17 veaux sur 30 (57%) pour la tilmicosine contre 7 sur 26 (27%) pour le florfénicol ($P = 0.02$). Les gains quotidiens sur 90 jours étaient de 1,55 kg/jour pour les veaux traités au florfénicol contre 1,51 kg/jour pour ceux traités à la tilmicosine. Aucune réaction indésirable significative n’a été notée et cela pour les 2 drogues. Les résultats indiquent que le florfénicol et la tilmicosine sont comparables dans le traitement du complexe respiratoire bovin dans l’Ouest canadien.

(Traduit par docteur André Blouin)


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Introduction

Bovine respiratory disease is a multifactorial disease resulting from the complex interaction of bacterial and viral agents, environmental conditions, management factors, and the animal (1). Respiratory disease is a common cause of illness and death in feedlot cattle in North America (2), with reported treatment rates of 13% to 26% (3), and proportional mortality rates of 31% to 71% (2,3). Prophylactic measures, such as vaccination or antibiotic medication of calves when they arrive at the feedlot, may reduce the incidence and severity of respiratory disease (3–6), but a large number of cattle ultimately require individual treatment.

Typically, undifferentiated bovine respiratory disease (UBRD) is treated with one or more antibiotics. The selection of an antibiotic is usually based on a combination of perceived efficacy, cost, ease of administration, availability, toxicity, and length of withdrawal time (7). Susceptibility of the important pathogens to the various antimicrobials might also be considered when deciding on therapy, because resistance to these drugs has been encountered (8). However, controversy exists regarding the correlation between the sensitivity of pathogens isolated from nasal swabs in culture and the sensitivity of the actual pathogen in the lung (8–10). The findings of the clinical microbiology laboratory and the pharmacokinetic considerations of the drug involved do not necessarily correlate with therapeutic outcome (7,9). A properly designed clinical trial utilizing spontaneously occurring disease is therefore the most effective method to evaluate the efficacy of an antimicrobial for treatment of a particular disease (9).

Florfenicol [D-d-threo-3-fluoro-2-dichloroacetamidino-1-(4-methylsulfonylphenyl)-1-propanol] is a structural analog of thiamphenicol and chloramphenicol, whose chemical structures are shown in Figure 1 (11). All 3 compounds fit into the same bacterial receptor sites and thus have an identical antibacterial mechanism of action (12). These drugs inhibit bacterial growth through inhibition of peptidyl transferase, thereby interfering with bacterial protein synthesis (13). The pharmacokinetic parameters of florfenicol, which include excellent concentrations in bronchial secretions, make it a reasonable choice for the treatment of UBRD (14).

Chloramphenicol has been associated with 2 types of bone marrow suppression in man; a dose-related reversible suppression of erythropoiesis due to inhibition of mitochondrial protein synthesis and a rare dose-independent idiosyncratic response resulting in bone marrow aplasia and possible leukemia (15). The non-dose-related aplastic anemia, attributed to the nitro group (16,17), was the major reason that the use of this drug in farm animals was banned. Neither florfenicol nor thiamphenicol contains the nitro group, thus aplastic anemia has not been associated with their administration.

Florfenicol has been shown to have greater in vitro potency against pathogenic bacteria than either chloramphenicol or thiamphenicol (18,19), and also has activity against some bacteria that are resistant to chloramphenicol. Resistance to chloramphenicol and thiamphenicol is usually related to plasmid-mediated production of a chloramphenicol acetyltransferase that acetylates the 3'-hydroxyl group (20,21). Replacing the hydroxyl group at position 3 with a fluorine atom allows the compound to maintain antibacterial activity in the face of the acetyltransferase enzyme.

Since its introduction to the Canadian marketplace in 1990, the use of the semisynthetic macrolide antibiotic tilmicosin (Micotil, Provet Division, Eli Lilly Canada, Guelph, Ontario) has become widespread for the treatment of naturally occurring bovine respiratory disease because of its one dose, low volume, convenience and efficacy (22). The objective of this study was to evaluate the field efficacy of florfenicol (Nuflor, Schering-Plough Animal Health, Schering Canada, Pointe Claire, Quebec) for the treatment of naturally occurring UBRD by comparison with tilmicosin under conditions typical of western Canadian feedlots.

Materials and methods

Auction market-derived beef calves of mixed breeds that appeared to be at least 5 mo of age were purchased by an order buyer between November 15 and December 8 and transported to the study center, where they were processed according to a specified protocol. This included unique individual animal identification, modified live infectious bovine rhinotracheitis, parainfluenza-3 virus vaccination (Coopers IBR/PI3, Mallinckrodt, Pointe Claire, Quebec), vitamin AD injection (Poten A.D., rogar/STB, London, Ontario), anthelmintic therapy (Ivomec Pour-On, Merck Agvet, Merck Frosst Canada, Kirkland, Quebec), multivalent clostridial vaccination (Tasvax-7, Mallinckrodt), and a growth implant (Synovex S or H, Syntex Animal Health, Oakville, Ontario). Approximately 2000 calves received this specific processing protocol. The calves were then placed in open-air dirt pens of approximately 300 head capacity.

Feedlot personnel checked the pens twice daily and removed cattle based on their subjective determination of “depression.” Selected cattle entered the trial if they weighed more than 200 kg, had a rectal temperature equal to or greater than 40.5°C, and had no clinical signs attributable to organ systems other than the respiratory system within 14 d after arrival at the feedlot.
Each day, calves were ranked from highest to lowest temperature, and randomly assigned alternately to either the florfenicol or the tilmicosin group.

A deep nasal swab was taken from every calf entering the trial. These samples were stored in liquid nitrogen and subsequently cultured for growth of bacteria and mycoplasma. Minimum inhibitory concentrations (Sensititre, Micro Bio-Tech, Mississauga, Ontario) were determined for pathogenic organisms.

Calves were weighed for calculation of the treatment dose upon entering the trial and again approximately 90 d after entry into the feedlot. Florfenicol (300 mg/mL) was administered twice at 48-hour intervals at a dose of 20 mg/kg bodyweight (BW), IM, in the neck. Tilmicosin (300 mg/mL) was administered once at a dose of 10 mg/kg BW, SC. Following treatment, the calves were commingled in a pen. A scoring system was developed to evaluate a number of clinical parameters. These included illness index (0 = normal, 1 = slightly ill, 2 = moderately ill, 3 = severely ill, 4 = moribund), nasal discharge (0 to 2), dyspnea (0 to 2), and degree of rumen fill (0 to 2), with higher scores representing greater disease severity. The total clinical score was the sum of the 4 categories, with a maximum score of 10. Clinical scores and rectal temperatures were evaluated daily by the investigators until 24 h after therapeutic blood levels were assumed to have subsided, which was 48 h after the 2nd treatment with florfenicol, and 72 h after treatment with tilmicosin.

Calves were observed daily for adverse reactions to treatments for the duration of the study. This involved individually handling and palpating the animals for the first 5 or 6 d of the trial, and subsequently observing the calves in their pens. Any adverse reaction, including pain upon digital pressure and swelling at the site of injection, was recorded.

Clinical measurements of efficacy included mortality, rectal temperature, clinical scores, number of treatment failures, and number of relapses. A calf was defined as a treatment failure if it died, or if, on the last day of monitoring, it had an illness index score equal to or greater than 2 or a temperature equal to or greater than 40.0°C. A relapse was defined as a calf that had been treated, returned to its home pen, and diagnosed with respiratory disease at a later date. Calves that relapsed were treated with the same antibiotic that was originally administered for a maximum of 2 relapses. If a calf relapsed a 3rd time, it was treated with a different antimicrobial (neither tilmicosin nor florfenicol) and removed from the trial. Calves were monitored for treatment failure, relapse, and mortality for 28 d. A complete postmortem was performed on any calf that died during this period, and appropriate samples were submitted to the Diagnostic Laboratory at the Western College of Veterinary Medicine for bacteriologic and histopathologic examination. Performance data were assessed, based on average daily weight gains from day 0 to day 90.

### Table 1. Results of a trial comparing florfenicol with tilmicosin for treatment of undifferentiated bovine respiratory disease

<table>
<thead>
<tr>
<th></th>
<th>Florfenicol</th>
<th>Tilmicosin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number on trial</td>
<td>112</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>6 (5.4)*</td>
<td>11 (10.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>feeding period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>3 (2.7)</td>
<td>7 (6.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>study period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failures</td>
<td>18 (16.1)</td>
<td>27 (25.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>At least 1 relapse</td>
<td>33 (29.8)</td>
<td>35 (33.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>At least 2 relapses</td>
<td>7 (26.9)</td>
<td>17 (56.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>At least 3 relapses</td>
<td>2 (33.3)</td>
<td>7 (50.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>Average daily gain (kg/d)</td>
<td>1.55</td>
<td>1.51</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are percentage of cases

Results

Two hundred and twenty cattle entered the trial between November 18 and December 18, 1994, 112 received florfenicol and 108 tilmicosin (4 calves were removed before completion of the trial after developing a castration wound infection). Results are summarized in Table 1. The only statistically significant difference between the 2 treatment groups was in the number of calves that relapsed at least twice. Seventeen of 30 (57%) calves treated with tilmicosin had at least 2 relapses, compared with 7 of 26 (27%) calves treated with florfenicol (P = 0.02). (Deaths and treatment errors reduced the number at risk for 2nd relapse.) There were fewer treatment failures in the florfenicol-treated calves (16.1% versus 25.0%), but this difference was not statistically significant at the standard 5% level (P = 0.10). Treatment failures for florfenicol-treated calves were due to death (3), failure on illness index (1), failure on temperature (8), and failure on both illness index and temperature (6). Treatment failures for tilmicosin-treated calves were due to death (7), failure on illness index (3), failure on temperature (11), and failure on both illness index and temperature (6).

The daily mean rectal temperature of each group is shown in Figure 2. The average temperature at the start of the trial was 41.2°C for both treatment groups. Both

Statistical analysis

Data were entered and analyzed in a statistical software package for microcomputers (Statistix version 4.1, Analytical Software, Tallahassee, Florida, USA). Fisher's exact test was used for evaluating differences in mortality between the 2 groups (23). Chi-square tests of independence (24) and Fisher’s exact tests were used for evaluating differences between groups with respect to the number of relapses and treatment failures. Paired t-tests were used to compare day 0 and day 1, day 2, and day 4 rectal temperatures within groups (25). Normality of distribution was evaluated by graphical methods, and equality of variance was evaluated using Bartlett’s test. A 2-sample t-test compared the difference in the temperature decrease between the 2 groups (25). A 2-sample t-test was used to compare the difference in average daily gain between the 2 groups. The Wilcoxon rank sum test was used to examine differences between the groups with respect to the ordinal variables that were measured, such as total clinical score, illness index, nasal discharge, depression, and rumen fill (23). Relative risk and precision based 95% confidence intervals (C1) were calculated (26).
antibiotics significantly reduced the mean rectal temperature within 24 h after treatment ($P < 0.001$). There were no significant differences in the degree of temperature change between groups on any day.

Performance parameters were not significantly different. One hundred and seventy-two calves were available to be weighed at approximately 90 d after entry into the feedlot (mean number of days = 90.4, range = 58 to 107 d). Ninety-one florfenicol calves weighed 436.2 kg and 81 tilmicosin calves weighed 432.8 kg at this time, for average daily gains of 1.55 kg/d and 1.51 kg/d, respectively ($P = 0.44$).

There were no statistically significant differences between treatment groups with regard to any of the clinical parameters assessed at any time, whether examined in isolation or combined to create a total clinical score (Figure 3). On day 0, the florfenicol and tilmicosin groups both had combined mean clinical scores of 3.7. On day 1, the scores were 1.1 and 0.9, respectively. Both drugs reduced clinical signs by equal amounts. No detectable evidence of pain or swelling at the site of injection was noted with either drug treatment.

During the 28-day study period, 10 deaths occurred; 7 in the tilmicosin group and 3 in the florfenicol group. This difference was not statistically significant ($P = 0.20$). For tilmicosin-treated calves, 2 deaths were associated with bovine viral diarrhea virus infection (1 with a co-infection of Pasteurella haemolytica), 2 were consistent with Haemophilus somnus infection, 2 were attributed to Mycoplasma bovis infection, and 1 was attributed to P. haemolytica infection. For florfenicol-treated calves, 1 death was attributed to an adenovirus infection, 1 was attributed to bovine respiratory syncytial virus infection, and 1 was consistent with P. haemolytica infection. A total of 17 deaths occurred among test calves between entry into the trial and slaughter; 11 treated with tilmicosin and 6 treated with florfenicol ($P = 0.18$). All the animals that died after the 28-day trial period had some degree of bronchopneumonia that contributed significantly to their death. Myocarditis was a common finding in several of the calves that died after the trial period (data not shown).

Pasteurella haemolytica was isolated from the nasal swabs of 12 calves. One of these calves died (treated with florfenicol). Pasteurella haemolytica was also isolated from 2 postmortem specimens, both from calves in the tilmicosin treatment group. One isolate was resistant to tilmicosin — a postmortem sample from a calf in the tilmicosin group. The minimal inhibitory concentration (MIC) for this isolate was 25 µg/mL, while the tilmicosin MIC for all other isolates was 6.25 µg/mL. Reported MIC values for florfenicol ranged from 0.125 to 1.0 µg/mL. One P. haemolytica isolate was resistant to trimethoprim/sulfadoxine, 3 were resistant to penicillin, 2 were resistant to oxacillin, and 12 were resistant to tylosin.

Pasteurella multocida was isolated from the nasal swab of 42 calves, none of which died. Two isolates were resistant to tilmicosin, 7 to trimethoprim/sulfadoxine, 4 to penicillin, 2 to tetracycline, 6 to oxacillin, 1 to gentamicin, and 40 to tylosin. One isolate was resistant to 7 different antibiotics, including tilmicosin. Minimum inhibitory concentrations for florfenicol ranged from 0.25 to 2 µg/mL.

Mycoplasmas, many of which were not typeable, were isolated from a number of calves. Mycoplasmas were grown from nasal swabs of 94 calves, 3 of which died. Mycoplasmas were also grown from 7 postmortem specimens. Haemophilus somnus was not isolated from any of the nasal swabs or postmortem specimens; however 2 postmortem specimens had myocardial lesions characteristic of those associated with H. somnus infection.

Discussion

In this trial, florfenicol and tilmicosin were equivalent in limiting death loss and reducing clinical signs associated with UBRD. Theoretically, a negative control group should also have been included for comparison, but this had already been done in previous trials and also raised animal welfare considerations. The case fatality rate during the 28-day trial period was 4.5% (10/220), and over the first 90 d of the feeding period was 7.7% (17/220). This compares favorably with 2 other therapeutic trials (7.9) that compared penicillin, oxytetracycline, and trimethoprim-sulfadoxine, or trimethoprim-sulfadinoxine and ceftiofur and reported case fatality rates of 8.3% during a 60-day study period.
and 6.2% during a 90-day study period, respectively. The results of several trials using tilmicosin as the treatment were combined and gave mortality rates of 22.6% in negative control animals, and 4%, 1.3%, and 2.7% in calves treated with 5, 10 or 20 mg/kg BW of tilmicosin, respectively (22).

The only statistically significant difference found in this trial was fewer calves that relapsed at least twice in the group treated with florfenicol. This result may be biased, however, since florfenicol calves that had been treated twice were medicated for 2 more days than were the tilmicosin calves and, therefore, had less time “at risk” to relapse a 2nd time during the limited 28-day trial period.

All of the calves that died while on trial had pulmonary lesions; however, it could be argued that there were very few deaths that might have been prevented by treatment with antibiotics, since viral etiologies were common amongst several of the dead calves. However, the most important outcome measure in the trial was case fatality rate.

There was a trend toward fewer deaths in calves treated with florfenicol ($P = 0.20$), but the sample size was too small for this difference to be considered statistically significant. Prior to the trial, it was calculated that approximately 162 animals per group would be required to have an 80% chance of detecting differences of 75% or greater in mortality rates between the 2 treatment groups (24). For the difference in mortality rates found in this trial (6.5% in tilmicosin group versus 2.7% in florfenicol group) to be considered statistically significant, 475 calves per group would have been required. The primary reason for the relatively small sample size was a reduction in the number of fall-placed calves at the appropriate time, which resulted in fewer than expected sick calves from those pens with limited processing during the trial period. Also, the morbidity rate of approximately 10% in these pens was somewhat lower than expected, partially due to the relatively high cutoff temperature for inclusion in the study. It is difficult to plan for such variables in trial design, especially when a commercial enterprise is used as the study location, rather than an experimental station where the economics is not necessarily an important consideration.

The relative risk of dying for the tilmicosin group compared with the florfenicol group was 2.42 (95%CI = 0.64 to 9.12); that is, our “best estimate” is that calves treated with tilmicosin had 2.42 times the risk of dying compared with florfenicol-treated calves. Since the 95%CI crosses 1.0, this estimate cannot be considered statistically significant. However, if the relative risk observed in this trial was found not to be a chance finding in future studies and was repeated in other feedlot situations, it is clinically important and would be economically important to feedlot owners. Therefore, further trials seem to be warranted to more accurately evaluate the potential mortality reduction from using florfenicol for treatment of UBRD.

The association between isolation of pathogenic organisms from nasal swabs and respiratory disease is uncertain, as both P. multocida and P. haemolytica are considered to be normal inhabitants of the bovine respiratory tract (27). Culture results from postmortem specimens were almost certainly altered by antibiotic therapy. Isolation of mycoplasmas from nasal swabs and postmortem samples has been shown previously (10,28), but there is debate as to the pathogenicity of these organisms in relation to UBRD (10).

Clinical trials using florfenicol to treat naturally occurring bovine respiratory disease have been described. European trials have compared the efficacy of 20 mg/kg BW florfenicol to 15 mg/kg BW amoxicillin each given twice, 48 h apart (29,30). The larger of these 2 studies (29) included 269 cattle, 3 to 9 mo of age, in 5 separate groups. All clinical parameters of respiratory disease improved with both treatments; however, the improvement was faster in the florfenicol group. During the first 10 d, 50% of the animals in the amoxicillin group were considered to be treatment successes, while 85% of the animals receiving florfenicol were considered treatment successes. This difference was statistically significant. Results were similar in a smaller trial (30), with florfenicol treatment resulting in fewer treatment failures and reinfections or relapses. North American studies have compared the use of florfenicol with daily administration of 10 mg/kg BW oxytetracycline for 4 consecutive days (31). The results of 4 clinical field trials were combined. Only 2 of 278 (0.7%) calves treated with florfenicol died of acute pneumonia, compared with 14 of 138 (10.1%) oxytetracycline-treated animals ($P < 0.0001$). Therapy was deemed successful in 79.9% of florfenicol-treated calves and 34.1% of oxytetracycline-treated calves at 1 wk posttreatment ($P < 0.0001$).

The current recommended dosage of florfenicol requires 2 treatments administered 48 h apart. The intramuscular half-life of florfenicol has been reported to be 18.3 h, with a range of 8.3 to 44 h (32), indicating slow release and absorption from the injection site. A 2 dose regimen of treatment will likely require keeping treated animals in a hospital pen for easy access for administration of the 2nd dose. This will make treating sick animals less convenient than treating with 1 injection of tilmicosin. However, by running the animal through the chute a 2nd time, the feedlot personnel may be better able to evaluate response to therapy. Florfenicol is administered IM, which makes it less convenient to administer than tilmicosin and increases the potential for injection site lesions at slaughter. No local injection site reactions were observed with either treatment in this trial.

If further studies confirm the trend toward lower mortality in florfenicol-treated calves that was found in this trial, florfenicol will become an important alternative therapy for treating UBRD in western Canada.

Acknowledgments

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References


