

A Comparison of Florfenicol–Flunixin Meglumine versus Tulathromycin for the Treatment of Undifferentiated Fever in Fall-Placed Feedlot Calves*

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CLINICAL RELEVANCE

The purpose of this study was to compare the efficacy of a new combination drug, florfenicol–flunixin meglumine, with tulathromycin for initial treatment of undifferentiated fever (UF) in fall-placed calves that received metaphylactic tilmicosin on arrival at the feedlot. No significant differences were observed in UF relapses between the two drugs. Calves treated with florfenicol–flunixin had a lower crude case fatality rate ($P = .0447$) than calves treated with tulathromycin but did not have a significantly lower respiratory disease and histophilosis case fatality rate ($P = .12$). Whether the new florfenicol–flunixin product is more cost-effective than tulathromycin for the treatment of UF in fall-placed feedlot calves will depend on how the new product is priced in the marketplace relative to tulathromycin.

■ INTRODUCTION

Numerous parenteral antimicrobials are available to treat bovine respiratory disease (BRD) in cattle, including procaine penicillin, oxytetracycline, trimethoprim–sulfadoxine, tilmicosin, erythromycin, spectinomycin, ampicillin, enrofloxacin, danofloxacin, ceftio-

fur, florfenicol, and tulathromycin.¹ The use of antiinflammatory drugs in conjunction with antimicrobials in the treatment of bacterial pneumonia in cattle is controversial.² Corticosteroids such as dexamethasone are generally not recommended by feedlot veterinarians in the treatment of BRD because of their strong

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immunosuppressive effects, which may lead to more relapses, chronics, and deaths.^{1,2} The efficacy of NSAIDs in the treatment of BRD has not been well documented in clinical trials in North America.²⁻⁴ Flunixin meglumine is an NSAID that has been used in combination with florfenicol in Europe (Resflor, Intervet/Schering-Plough Animal Health, United Kingdom) for the treatment of BRD.⁵⁻⁹ In animals with BRD, flunixin meglumine is believed to help reduce the intensity of the pathologic inflammatory reaction caused by such mediators as cytokines and neutrophils.^{7,8}

Resflor, as available in Europe, contains 300 mg/ml of florfenicol and 16.5 mg/ml of flunixin meglumine.⁹ Florfenicol (Nuflor, Intervet/

donic acid to cyclic endoperoxides.⁷⁻⁹ Consequently, synthesis of eicosanoids—important mediators of the inflammatory process involved in central pyrexia, pain perception, and tissue inflammation—is inhibited. Flunixin exerts its antipyretic effect by inhibiting prostaglandin E₂ synthesis in the hypothalamus. Although flunixin has no direct effect on endotoxins after they have been produced, it reduces prostaglandin production and hence reduces the many effects of the prostaglandin cascade. Prostaglandins are part of the complex processes involved in the development of endotoxic shock.⁹

Tulathromycin (Draxxin Injectable Solution, Pfizer Animal Health, Quebec, Canada) is a macrolide antibiotic that binds to the bac-

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Schering-Plough Animal Health, Quebec, Canada) is a fluorinated derivative of thiamphenicol. It is a broad-spectrum antibiotic with a label claim of activity against common bacterial pathogens in BRD, such as *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. It inhibits protein synthesis by binding to ribosomal subunits of susceptible bacteria.

Flunixin meglumine (Banamine Sterile Solution Injectable, Intervet/Schering-Plough Animal Health, Quebec, Canada) is labeled as a potent nonnarcotic, nonsteroidal analgesic agent with antiinflammatory activity. It has been shown to have some analgesic effects in cattle.¹⁰ Flunixin meglumine acts as a reversible nonselective inhibitor of cyclooxygenase, an important enzyme in the arachidonic acid cascade pathway responsible for converting arachi-

terial ribosomal subunit, thereby inhibiting protein synthesis. It has in vitro activity against commonly isolated bacterial and mycoplasma pathogens involved in BRD, including *M. haemolytica*, *P. multocida*, *H. somni*, and *Mycoplasma bovis*.¹¹

The purpose of this study was to compare the efficacy of the new combination drug, florfenicol–flunixin, with tulathromycin when tilmicosin was used as the metaphylactic antimicrobial during on-arrival processing in moderately risked fall-placed feedlot calves.

■ **MATERIALS AND METHODS**

Florfenicol and tulathromycin are approved in Canada for the treatment of BRD; Resflor is not approved for use in Canada. An Experimental Studies Certificate was applied for and

received from Health Canada to conduct the field trial. Approval by an Animal Use Committee is not required in field trials conducted in commercial facilities.

Trial Facilities

The study was conducted in southern Alberta during the fall of 2007 on two large commercial feedlots under similar management systems; the one-time capacity was 14,000 head in one feedlot and 25,000 in the other. The feedlots contained both calves and yearlings, all of which were fed to slaughter. Cattle were housed in open, dirt feedlot pens with windbreak fences on three sides and a feed bunk with a cement apron on the fourth side. Pens held approximately 225 head. Cattle were fed a balanced ration consisting of barley or corn grain, corn or barley silage, corn dried distillers grains with solubles, and a mineral–vitamin supplement.

Study Animals

Animals enrolled in the study were crossbred beef steer (yard 1) and heifer (yard 2) calves (weight range, 295 to 340 kg) purchased from auction markets throughout Canada between December 12, 2007, and January 15, 2008. Within 24 hours of arrival at the feedlot, calves were processed and treated according to the facility's standardized animal health protocols, which were the same for both feedlots.

During on-arrival processing, calves were vaccinated with a modified-live virus vaccine containing bovine rhinotracheitis virus and two types of bovine viral diarrhea virus (types 1 and 2) (Vista 3 SQ, Intervet Canada); an *M. haemolytica* and *H. somni* bacterin (Somnu-Star Ph, Novartis Animal Health Canada); and a clostridial bacterin–toxoid (steers: Tasvax 8, Schering-Plough Animal Health; heifers: Vision 8 with Spur, Intervet Canada). They were also treated with an antiparasitic (Ivermax

Pour-On, RXV) and administered a growth-promoting implant (Synovex C, Wyeth Animal Health). The cattle were fed monensin sodium throughout the feeding period to control coccidiosis and bloat and tetracycline for the first 56 days on feed (DOF) to control hemophilosis. Calves received metaphylactic therapy with tilmicosin (Micotil, Elanco Animal Health, Ontario, Canada; 10 mg/kg SC in the neck region). There was a 5-day postmetaphylactic interval set for tilmicosin after on-arrival processing (i.e., pen riders could not pull and treat cattle for undifferentiated fever [UF] during the 5-day moratorium). The postmetaphylactic interval was set by the feedlot veterinarian and was part of the standard health protocol. All cattle were identified with a unique feedlot tag number and a Canadian Cattle Identification Agency ear tag.

Experimental Design

Feedlot pen riders monitored feedlot calves twice daily in their pens. Cattle exhibiting clinical signs of BRD, including anorexia, depression, abnormal respiration, nasal discharge, and/or coughing, were removed from their pen and examined at the treatment facility. Those with clinical signs of BRD and a rectal temperature $\geq 104.0^{\circ}\text{F}$ ($\geq 40^{\circ}\text{C}$) were assigned to the study and defined as UF. Calves that had a history of treatment for any previous disease or were moribund were excluded from the trial.

The target sample size for this trial was 250 animals/treatment group, a balance between trial power and practical and economic logistics of conducting the study. In moderate-risk calves metaphylactically treated on arrival with Micotil, a first-pull BRD treatment rate of 25% is not uncommon in calves from the feedlots studied here. To reliably detect (power = 80%) a significant difference ($P < .05$) in first-pull BRD treatment rates between treatment groups of 25% and 15%, approximately 250

animals/treatment group is required. Similar sample sizes have been used to detect statistically significant BRD outcomes between treatment groups in fall-placed feedlot calves.^{12,13}

Cattle were systematically randomized to treatment group within each feedlot. A coin was flipped to determine whether the first animal in the trial would be treated with florfenicol–flunixin or tulathromycin. The next animal was treated with the other drug. On January 15, 2008, allocation of new cattle to

vetrin, Schering-Plough Animal Health; 16 mg/kg IM in the neck region for 3 to 5 days). Third UF relapses were deemed chronics and were not treated; instead, they were sent to the chronic pen and managed according to the feedlot's chronic pen management protocol. All other diseases were treated according to a standard feedlot protocol.

All treatment data, including animal identification, treatment date, presumptive diagnosis, drug used, animal weight, dose, and route,

There were no statistically significant differences between florfenicol–flunixin and tulathromycin in first, second, or third UF relapse rate.

the trial was stopped because fall-placed calves were no longer entering the feedlots.

The treatment groups were as follows:

- Florfenicol–flunixin (Resflor; 300 mg/ml florfenicol and 27.4 mg/ml flunixin meglumine), 2 ml/15 kg SC in the neck region
- Tulathromycin (Draxxin), 2.5 mg/kg SC in the neck region

Calves were returned to their pen after being treated. Feedlot pen riders were blinded to the experimental status of each animal. Trial calves that were subsequently pulled by the pen riders for UF qualified for relapse treatment only if they had exceeded the assigned posttreatment interval of 5 days for both drugs. Animals exhibiting clinical signs of depression, anorexia, abnormal respiration, nasal discharge, and/or cough, regardless of rectal temperature, were diagnosed as UF relapses. First UF relapses were treated with enrofloxacin (Baytril 100, Bayer Animal Health; 7.7 mg/kg SC in the neck region), and second UF relapses were treated with trimethoprim–sulfadoxine (Tri-

were recorded in the animal health management software system (DG Professional, ComputerAid Professional Services Ltd., Okotoks, Alberta, Canada) on a chute-side computer. Trial cattle were followed from allocation until slaughter. Any adverse events, such as anaphylactic reactions or sudden death following the administration of the antimicrobials, were recorded. All mortalities were necropsied by the feedlot veterinarian to determine cause of death based on gross pathology.

Data Analysis

Data were analyzed using analytical software programs (SAS System for Windows, Release 9.1, SAS Institute, Cary, NC). UF relapse rates were defined as previously described.^{11,12} Crude case fatality¹⁴ was defined as the proportion of UF cases (i.e., animals allocated to the study that met the case study definition of UF) that died; BRD case fatality was the proportion of UF cases that died of respiratory disease (fibrinous pneumonia and/or bronchopneumonia); and the case fatality from respiratory disease or histophilosis (BRDHS) was the proportion of

TABLE 1. Animal Health Data in Fall-Placed Steer Calves from Allocation to Slaughter

<i>Outcome</i>	<i>Experimental Group</i>		<i>Relative Risk</i>	<i>90% CI</i>	<i>P Value</i>
	<i>FLOR–FLU</i>	<i>TULA</i>			
UF	228	227			
1st UF relapse	25 (11%)	16 (7%)	1.56	0.95–2.73	.145
2nd UF relapse	7 (28%)	3 (19%)	1.47	0.71–5.28	.510
3rd UF relapse	0 (0%)	0 (0%)	—	—	—
Crude CFR*	2 (0.9%)	8 (3.5%)	0.25	0.09–0.92	.047
BRD CFR [†]	2 (0.9%)	5 (2.2%)	0.40	0.13–1.59	.275
BRDHS CFR [‡]	2 (0.9%)	7 (3.1%)	0.29	0.10–1.09	.125

*The proportion of UF that died.

[†]The proportion of UF that died of respiratory disease.

[‡]The proportion of UF that died of respiratory disease or histophilosis.

BRD = bovine respiratory disease; BRDHS = BRD or histophilosis; CFR = case fatality rate; FLOR–FLU = florfenicol–flunixin meglumine; TULA = tulathromycin; UF = undifferentiated fever.

UF cases that died of either respiratory disease or histophilosis (i.e., myocarditis, pleuritis, pneumonia/arthritis) based on gross necropsy findings.

Differences in UF relapse rates and case fatality rates between florfenicol–flunixin and tulathromycin groups were analyzed using generalized linear mixed modeling techniques (PROC GLIMMIX, SAS Institute) to account for the clustering of calves within pens and feedlots, with both variables treated as random effects. A binomial data distribution and logit link function were used in the modeling procedure. Calculation of Wald-type CIs was done by using pseudo-likelihood estimation. The parameter estimates and CIs were converted to relative risks as previously described.¹⁵ Individual animals were the unit of analysis. The 10% level of statistical significance was used for all tests.

Multivariate quantile regression analyses were completed (PROC QUANTREG, SAS Institute) to compare the median DOF at treatment allocation, median days between initial treatment and first UF relapse, median

days between first and second UF relapses, and median days between initial treatment and death between each treatment group. The clustering of calves within pens and feedlots was accounted for by including each variable as a fixed effect in all four models. Parameter estimates and 90% CIs were estimated using an interior point algorithm and the Markov chain marginal bootstrap method, respectively. The significance of each factor was assessed using both Wald and likelihood ratio tests.

■ RESULTS

A total of 462 animals were allocated to the trial. Seven animals were removed from the dataset for failure to follow the postmetaphylactic interval for tilmicosin. There were no significant differences in the number of removals from either treatment group. The final data set contained 228 animals in the florfenicol–flunixin group and 227 animals in the tulathromycin group.

Results are presented in Table 1. There were no statistically significant differences between florfenicol–flunixin and tulathromycin in first,

second, or third UF relapse rate. The crude case fatality rate was significantly lower ($P = .047$) in the florfenicol–flunixin group than in the tulathromycin group. Three animals died in the florfenicol–flunixin group: one each of chronic bronchopneumonia and pleuritis, fibrinous pneumonia, and mucosal disease. Eleven animals died in the tulathromycin group: three of fibrinous pneumonia, two of interstitial pneumonia, two of chronic bronchopneumonia and arthritis, and one each of arthritis, mucosal disease, pericarditis, and an unknown cause. The median DOF at the time of mortality was 32 days for the florfenicol–flunixin group and 25 days for the tulathromycin group. The median days between first UF treatment and death was

■ DISCUSSION

This study suggests that florfenicol–flunixin is more effective than tulathromycin in reducing crude case fatality rates for initial UF treatment in moderate-risk fall-placed steer and heifer calves when the calves are given metaphylactic tilmicosin during on-arrival processing at the feedlot. However, some of the causes of death observed here, such as mucosal disease and interstitial pneumonia, would not be responsive to antimicrobial therapy. If deaths due to mucosal disease and interstitial pneumonia are removed from the analysis, then the differences in case fatality between the two treatment groups was significant ($P = .076$). These results were consistent with recent

If deaths due to mucosal disease and interstitial pneumonia are removed from the analysis, then the differences in case fatality between the two treatment groups was significant ($P = .076$).

26 days for the florfenicol–flunixin group and 14 days for the tulathromycin group. There were no significant differences between the two treatment groups in the BRD or BRDHS case fatality rates, DOF when pulled for UF, DOF at the time of mortality, days between initial treatment for UF and death, or posttreatment intervals.

The median DOF when first pulled for UF was 10 days for the florfenicol–flunixin group and 9 days for the tulathromycin group. The posttreatment interval between initial treatment and first UF relapse was 10 days for the florfenicol–flunixin group and 6 days for the tulathromycin group. The posttreatment interval between first and second UF relapses was 9 days for the florfenicol–flunixin group and 7 days for the tulathromycin group.

findings comparing florfenicol with tulathromycin for initial UF treatment in feedlot calves after metaphylactic administration of tulathromycin or tilmicosin.^{12,13} Although the number of relapses in the florfenicol–flunixin group was higher, the difference was not statistically significant in this study ($P = .145$); this finding warrants further investigation in a larger population of feedlot cattle.

Whether the addition of flunixin meglumine to florfenicol in Resflor improves the clinical response in feedlot calves over florfenicol alone in BRD is not known because there was no comparative treatment group receiving florfenicol alone. Failure to show statistically significant differences in some animal health outcomes, such as BRD and BRDHS case fatality rates, may be the result of too small a

sample size at these disease risks (type 2 error).¹⁴ Disease risks were lower than historically observed in these feedlots. We estimated that the power of our current study ranged between 20% and 60% for the mortality outcomes.

All cattle in this study received chlortetracycline in the feed for the first 56 DOF to control histophilosis. The tetracycline in the feed in combination with metaphylactic tilmicosin may have reduced overall disease risks in both treatment groups, reducing our ability to detect statistically significant differences in some health outcomes between the two treatment groups with the current sample size.

There was one case of mucosal disease in both treatment groups. The effect of cattle persistently infected with bovine viral diarrhea virus on the incidence of BRD in feedlots in these cattle is unknown; however, given that there was one case of mucosal disease in each treatment group, it is unlikely that bovine viral diarrhea virus was a confounding factor in this study.

The cattle in this study received metaphylactic tilmicosin on arrival. Tilmicosin and tulathromycin are both macrolides. It is unknown whether previous treatment with tilmicosin may have reduced the sensitivity of the bacterial pathogens to tulathromycin.

Additional, larger controlled field trials in feedlot calves at risk for BRD should be conducted to add reliability to the findings presented here. Also, clinical feedlot trials should be conducted to compare florfenicol with florfenicol–flunixin to determine whether the addition of the NSAID improves the treatment response to florfenicol alone. If possible, these trials should include performance and carcass outcomes. According to its label claim, flunixin reduces pyrexia, endotoxemia, and inflammation. It would be interesting to see whether these effects are manifested as both clinically and economically significant improvements in feedlot growth performance and/or carcass grades.

Florfenicol–flunixin is not currently commercially available in Canada; therefore, the cost of the product is unknown. As a result, we could not conduct an economic assessment of the cost–benefit of florfenicol–flunixin in comparison with tulathromycin.

■ CONCLUSION

The results of this study suggest that florfenicol–flunixin is more effective than tulathromycin in reducing crude case fatality rates in the initial treatment of UF in fall-placed feedlot calves at low to moderate risk for BRD that receive metaphylactic tilmicosin on arrival at the feedlot.

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