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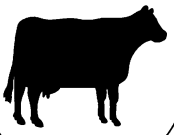

Evaluation of florfenicol for the treatment of undifferentiated fever in feedlot calves in western Canada

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Abstract — A study was conducted in western Canada to evaluate the efficacy of florfenicol for the treatment of undifferentiated fever (UF) in feedlot calves. One hundred and twenty-five recently weaned, auction market derived, crossbred, beef steer calves suffering from UF were allocated to 1 of 2 experimental groups as follows: florfenicol, which was intramuscular florfenicol administered at the rate of 20 mg/kg body weight at the time of allocation (day 0) and again 48 h later; or control, which was intramuscular saline administered at the same volume as florfenicol at the time of allocation and again 48 h later. Eighty-four calves were allocated to the florfenicol group and 41 calves were allocated to the control group.

Outcome measures describing animal health, body weight, and rectal temperature parameters were used to determine the efficacy of florfenicol for the treatment of UF.

The 1st relapse of UF, 2nd relapse of UF, overall mortality, bovine respiratory disease mortality, and haemophilosis mortality rates were significantly ($P < 0.05$) lower in the florfenicol group than in the control group. Animals in the florfenicol group were significantly ($P < 0.05$) heavier at day 15 and day 45 than animals in the control group. The rectal temperature on days 1, 2, 3, and 4 of animals in the florfenicol group was significantly ($P < 0.05$) lower than in the control group. In addition, the change in rectal temperature from day 0 to day 4 was significantly ($P < 0.05$) different between the experimental groups.

The results of this study demonstrate that florfenicol is an efficacious antimicrobial for the treatment of UF.

Résumé — Évaluation du florfénicol dans le traitement de fièvres non-spécifiques chez des veaux en parc d'engraissement dans l'ouest canadien. Une étude a été entreprise dans l'Ouest du canadien pour évaluer l'efficacité du florfénicol dans le traitement de fièvres non-spécifiques (FNS) chez des veaux en parc d'engraissement. Cent vingt-cinq veaux de boucherie, récemment sevrés, achetés à l'encan, de races croisées et souffrant de FNS ont été attribués à un des deux groupes expérimentaux. Le groupe du florfénicol recevait le médicament par voie intramusculaire à la dose de 20 mg/kg de poids corporel au moment de la formation du groupe (jour 0) et la même dose 48 h plus tard alors que le groupe témoin recevait un volume équivalent de saline par voie intramusculaire au moment de la formation du groupe et 48 heures plus tard. Quatre-vingt-quatre veaux faisaient partie du groupe du florfénicol et 41 veaux faisaient partie du groupe témoin.

Des paramètres destinés à décrire l'état de santé de l'animal, le poids corporel et la température rectale ont été utilisés pour déterminer l'efficacité du florfénicol dans le traitement des FNS. Les taux de première rechute de FNS, de deuxième rechute, de mortalité totale, de mortalité attribuée à la maladie respiratoire bovine et de mortalité reliée à l'hémophilose étaient significativement plus bas ($P < 0,05$) dans le groupe du florfénicol que dans le groupe témoin. Les animaux du groupe du

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Editor's comment — The Bureau of Veterinary Drugs, Health Canada, requires that in preliminary studies of a new antimicrobial, the negative control animals not be treated.

florfénicol étaient significativement plus lourds ($P < 0,05$) aux jours 15 et 45 que les animaux du groupe témoin. La température rectale aux jours 1, 2, 3 et 4 des animaux du groupe traité était significativement plus basse ($P < 0,05$) que celle du groupe témoin. De plus, l'évolution de la température rectale entre les jours 0 et 4 était significativement différente ($P < 0.05$) entre les deux groupes expérimentaux.

Les résultats de cette étude démontrent que le florfénicol est un antimicrobien efficace dans le traitement des FNS.

(Traduit par docteur André Blouin)

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Introduction

Florfenicol (Nuflor, Schering Canada, Pointe Claire, Quebec) is a new antimicrobial that has recently been approved for IM use in beef cattle and nonlactating dairy cattle. Florfenicol is an analogue of thiamphenicol that has very promising pharmacodynamic properties (1–3). The purpose of the study reported herein was to determine the effectiveness of florfenicol for the treatment of undifferentiated fever (UF) in feedlot calves.

Materials and methods

Trial facilities

The trial was conducted in a commercial feedlot in Airdrie, Alberta, which has a capacity of 16,000 animals. The basic design of this feedlot is representative of standard design in western Canada. Animals are housed in open air, dirt floor pens, arranged side by side with central feed alleys and 20% porosity fencing. There is a hospital facility located in the feedlot. The hospital is equipped with a hydraulic chute, an individual animal scale, a chute-side computer for animal health data, and separation alleys to facilitate the return of cattle to designated pens. Several open air hospital pens are located adjacent to the hospital. Also, there are an enclosed processing facility and several receiving pens.

Trial animals

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 to 10 mo of age and weighed between 212 kg and 360 kg. Upon arrival at the feedlot, the calves were moved through a hydraulic chute for a group of procedures known collectively as processing. In this process, all animals were ear tagged (to provide unique, individual animal identification), branded, implanted with a progesterone-estradiol growth implant (Synovex-S, Syntex Agribusiness, Mississauga, Ontario), and vaccinated against infectious bovine rhinotracheitis (IBR) and parainfluenza-3 (PI_3) viruses (IBR/PI_3, Coopers Agropharm, Ajax, Ontario). In addition, all animals received a *Pasteurella haemolytica* bacterial extract (Presponse, Langford, Guelph, Ontario), a multivalent clostridial vaccine (Tasvax 7, Coopers Agropharm), and topical ivermectin (0.5%) at the rate of 1.0 mL per 10 kg body weight (BW) (Ivomec Pour On, Merck AgVet, Kirkland, Quebec).

Three hundred and sixty-four calves that arrived at the feedlot from November 3, 1993, to November 10, 1993, were candidates for allocation to the study.

Experimental design

The appropriate number of animals to be included in the study was determined using mortality data that described the overall, BRD, and haemophilosis mortality rates occurring in treated and untreated feedlot calves (Booker, Jim, Guichon, unpublished observations). It was calculated that approximately 120 animals allocated in a 2 to 1 treated to untreated ratio would be required to have a 90% chance of detecting differences of 80% or greater in mortality rates between untreated and treated calves as statistically significant ($P < 0.05$) (True Epistat, Epistat Services, Richardson, Texas, USA).

Subsequent to the processing event, the animals were housed in a designated feedlot pen. A veterinarian and experienced feedlot personnel observed the animals once or twice daily for evidence of disease. Animals that were deemed to be "sick," based on subjective parameters, such as, general appearance and attitude, gauntness, reluctance to move, etc., were removed from the feedlot pen and presented to the hospital facility for examination and potential allocation to the study. In this study, animals were designated as suffering from UF when they had an elevated rectal temperature greater than or equal to 40.5°C for 2 consecutive days (day -1 and day 0) and an absence of abnormal clinical signs referable to organ systems other than the respiratory system. Calves that fulfilled the criteria for UF were weighed (day -1 and day 0) and allocated (day 0) to 1 of 2 experimental groups: florfenicol, to which florfenicol (Nuflor, Schering-Plough Animal Health, Schering Corporation, Union, New Jersey, USA) was administered IM at the rate of 20 mg/kg BW at the time of allocation and again 48 h later; or control, to which saline was administered IM at the same volume as florfenicol at the time of allocation and again 48 h later. Eighty-four calves were allocated to the florfenicol group and 41 calves were allocated to the control group. At the time of allocation (day 0), a transtracheal wash was performed and a nasal swab and a blood sample for microbiological culture were obtained from each animal. The rectal temperature of each animal was measured and recorded on days 1 to 4 of the study. Also, a blood sample for microbiological culture was taken from each animal on day 3.

All 125 florfenicol and control animals were sent to a designated feedlot pen after allocation where they were housed for the duration of the study. Animals were observed daily by experienced feedlot personnel for evidence of recurrent disease. Animals with recurrent disease were moved to the hospital facility and a diagnosis of an UF relapse was made if the rectal temperature was greater than or equal to 40.0°C and there was an absence of abnormal clinical signs referable to organ systems other than the respiratory system. Relapses in the

Table 1. Definition of the parameters utilized to assess animal health

First relapse of UF[a]	= (number of 1st relapses of UF divided by the number of animals initially treated for UF)	× 100%
Second relapse of UF	= (number of 2nd relapses of UF divided by the number of first relapses)	× 100%
Overall mortality	= (number of mortalities due to all causes divided by the number of animals initially treated for UF)	× 100%
BRD[b] mortality	= (number of BRD attributable mortalities divided by the number of animals initially treated for UF)	× 100%
Haemophilosis[c] mortality	= (number of haemophilosis attributable mortalities divided by the number of animals initially treated for UF)	× 100%
Miscellaneous mortality	= (number of mortalities due to causes other than BRD or haemophilosis divided by the number of animals initially treated for UF)	× 100%
Relative risk	= (risk for the control group divided by the risk for the florfenicol group)	× 100%

[a]UF is undifferentiated fever
[b]BRD is bovine respiratory disease
[c]Haemophilosis is disease due to *Haemophilus somnus* infection

florfenicol group were treated with IM florfenicol, at the same dose as on allocation, on the day of relapse and again 48 h later. Relapses in the control group were treated with IM saline, at the same dose as on allocation, on the day of relapse and again 48 h later. On days 15 and 45, all animals were weighed.

Animals that were moribund or became recumbent during the study were euthanized by attending feedlot veterinarians.

All dead animals were necropsied by attending feedlot veterinarians. Appropriate specimens for histology were submitted to a laboratory (Veterinary Pathology Laboratory, Edmonton, Alberta) for confirmation of the cause of death.

Microbiological procedures

The transtracheal wash, nasal swab, and the day 0 and day 3 blood samples were transported to a laboratory (Gard Microbiology Services, Airdrie, Alberta) and cultured for *Pasteurella haemolytica, Pasteurella multocida,* and *Haemophilus somnus.*

Data collection and management

The animal health, BW, microbiological culture, and histopathological data were entered into a spread sheet program (Quattro Pro for Windows — Version 5.00, Borland International, Scotts Valley, California, USA) and verified.

The mortality data were categorized into those attributable to bovine respiratory disease (BRD mortality), those attributable to *Haemophilus somnus* infection (haemophilosis mortality), and those attributable to causes other than BRD or haemophilosis (miscellaneous mortality) based on the results of the gross and histologic postmortem examinations. First relapse of UF, 2nd relapse of UF, overall mortality, BRD mortality, haemophilosis mortality, and miscellaneous mortality rates were calculated for each experimental group (Table 1). Initial BW was calculated as the average of the day -1 and day 0 BW. Similarly, the initial rectal temperature was calculated as the average of the day -1 and day 0 temperatures. The microbiological culture results were tabulated by sample source and pathogen.

Summary and comparison of the animal health, BW, microbiological culture, and rectal temperature data were used to determine the efficacy of florfenicol for the treatment of UF.

Statistical analysis

The data were analyzed using an analytic software program (The SAS System for Windows — 3.100, Release 6.08, SAS Institute, Cary, North Carolina, USA). For the various animal health indices defined in the previous section, relative risks (RR) and their 95% confidence intervals (95% CI) were calculated for the control group relative to the florfenicol group (4). Fisher's exact one-tailed tests were calculated for each relative risk to determine statistical significance (5). The BW data for day 0, day 15, and day 45 were compared between the experimental groups using least squares analysis of variance and covariance (6). The day 15 and day 45 BW were corrected for the effects of initial BW. The transtracheal wash, nasal swab, and blood culture results were evaluated for between experimental group differences using the Fisher's exact one-tailed test. The rectal temperature profile for the initial treatment regime for UF (day 0 to day 4) was evaluated for between experimental group differences using repeated measures analysis of variance, including univariate analyses for each observation day (6,7).

Results

There were 84 and 41 animals allocated to the florfenicol and control groups, respectively.

The 1st relapse of UF, 2nd relapse of UF, overall mortality, BRD mortality, and haemophilosis mortality rates were significantly ($P < 0.05$) lower in the florfenicol group than in the control group (Table 2). The cause specific mortality detail is presented in Table 3. Animals in the florfenicol group were significantly ($P < 0.05$) heavier at day 15 and day 45 than animals in the control group (Table 4). The rectal temperatures of animals in the florfenicol group were significantly ($P < 0.05$) lower than those in the control group on days 1, 2, 3, and 4. In addition, the change in rectal temperature from day 0 to day 4 was significantly ($P < 0.05$) different between the experimental groups (Table 5).

There was 1 positive day 0 blood culture in the florfenicol group (*Pasteurella multocida*) and 1 positive day 0 blood culture in the control group (*Pasteurella*

Table 2. Morbidity and mortality summary by experimental group

	Florfenicol (%)	Control (%)	Relative risk	95% CI[a]	*P*-value
First relapse of UF[b]	20.24	60.98	3.01	1.85–4.92	<0.001
Second Relapse of UF[b]	5.88	44.00	7.48	1.06–52.69	0.007
Overall mortality[b]	1.19	34.15	28.68	3.91–210.69	<0.001
BRD mortality[b]	0.00	19.51	34.41	2.03–581.90	<0.001
Haemophilosis mortality[b]	0.00	9.76	18.21	1.00–330.45	0.010
Miscellaneous mortality[b]	1.19	4.88	4.10	0.38–43.89	0.250

[a]95% CI is the 95% confidence interval calculated for each relative risk
[b]Refer to Table 1

Table 3. Cause specific mortality detail

Experimental group	Tag No.	Day of study	Postmortem Diagnoses: Gross examination	Postmortem Diagnoses: Histologic examination	Mortality category
Florfenicol	719	19	Musculoskeletal injury	No abnormal findings in tissues examined	Miscellaneous[a]
Control	706	2	Haemophilus myocarditis	Suppurative myocarditis with myocardial necrosis and vascular thrombosis	Haemophilosis[b]
	720	6	Fibrinous pneumonia	Fibrinous pneumonia, bronchitis, and bronchiolitis	BRD[c]
	729	6	Fibrinous pneumonia	Severe necrotizing bronchiolitis with alveolitis and fibrinous interlobular and pleural reaction	BRD
	734	15	Haemophilus septicemia	Focal perivascular intracerebral hemorrhage	Miscellaneous
	735	4	Fibrinous pneumonia	Acute fibrinous pneumonia	BRD
	739	1	Fibrinous pneumonia	Acute fibrinous pneumonia	BRD
	773	8	Fibrinous pneumonia	Necrotizing fibrinous pneumonia	BRD
	777	4	Haemophilus pleuritis	Acute supportive vasculitis, acute multifocal necrotizing bronchiolitis, and fibrinous pleuritis	Haemophilosis
	780	8	Fibrinous pneumonia	Fibrinous pneumonia	BRD
	796	3	Haemophilus myocarditis	Suppurative bronchopneumonia, suppurative myocarditis, myocardial necrosis, vascular thrombosis and vasculitis	Haemophilosis
	798	8	Fibrinous pneumonia	Fibrinous pneumonia	BRD
	802	12	Fibrinous pneumonia	Acute fibrinous pneumonia	BRD
	804	6	Haemophilus pleuritis	Acute to subacute interstitial alveolar reaction with bacterial bronchitis consistent with *Haemophilus somnus* infection	Haemophilosis
	814	4	Interstitial pneumonia	Diffuse interstitial and subpleural emphysema with secondary bacterial pneumonia due to aspiration	Miscellaneous

[a]Miscellaneous is mortality due to causes other than BRD or haemophilosis based on the gross and histologic postmortem examinations
[b]Haemophilosis is mortality due to *Haemophilus somnus* infection based on the gross and histologic postmortem examinations
[c]BRD is mortality due to bovine respiratory disease based on the gross and histologic postmortem examinations

haemolytica). There was 1 positive day 3 blood culture in each experimental group (*Pasteurella haemolytica*). *Haemophilus somnus* was not cultured from any of the blood cultures on day 0 or day 3. The transtracheal wash and nasal swab microbiological culture results are summarized in Table 6. There were no significant ($P \geq 0.05$) differences in *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus* culture rates between the experimental groups with respect to the transtracheal washes, nasal swabs, or blood cultures.

Discussion

The results of this study demonstrate that florfenicol is an efficacious antimicrobial for the treatment of UF because the animal health, BW, and rectal temperature parameters of the florfenicol group were significantly ($P < 0.05$) improved as compared with the control group. However, additional trials to compare florfenicol to other commercially available antimicrobials are required to determine the relative cost-effectiveness of florfenicol treatment regimes, because the definitive evaluation of an antimicrobial should be determined by utilizing spontaneously occurring cases in properly designed field trials (8).

In this study, the authors chose to utilize the term UF to describe the clinical syndrome that is often referred to as bovine respiratory disease (BRD) or "shipping fever." In our opinion, BRD is a very misleading clinical diagnosis that is utilized because of historical precedent. It appears that the rationale for the assumption that feedlot animals deemed to be "sick" are suffering from BRD is because BRD has been documented as the most important cause of mortality in North American feedlots (9–14). However, the observation that BRD mortality is the leading cause of death in feedlot animals is not *prima facie* evidence that BRD is the leading cause of morbidity. If this premise, which has become part of veterinary dogma, is correct for western Canada, it follows that the diagnosis given to animals that are deemed to be "sick" with a lack of abnormal clinical signs referable to

Table 4. Body weight summary by experimental group

	Florfenicol LS Mean, $s_{\bar{x}}$[a]	Control LS Mean, $s_{\bar{x}}$	*P*-value
Initial weight (kg)[b]	282, $s_{\bar{x}} = 3$	281, $s_{\bar{x}} = 4$	0.734
Day 15 weight (kg)[c]	299, $s_{\bar{x}} = 2$	283, $s_{\bar{x}} = 3$	<0.001
Day 45 weight (kg)[c]	344, $s_{\bar{x}} = 3$	321, $s_{\bar{x}} = 5$	<0.001

[a]The least squares mean and standard error calculated from the analysis of variance
[b]Initial weight is the average of the day -1 and day 0 weights ($n = 125$)
[c]The day 15 and day 45 weights have been adjusted for initial weight effects ($n = 110$)

Table 5. Rectal temperature summary by experimental group[a]

	Florfenicol LS Mean, $s_{\bar{x}}$[b]	Control LS Mean, $s_{\bar{x}}$	*P*-value
Day 0 (°C)[c]	40.9, $s_{\bar{x}} = 0.0$	41.0, $s_{\bar{x}} = 0.0$	0.057
Day 1 (°C)	39.7, $s_{\bar{x}} = 0.1$	40.9, $s_{\bar{x}} = 0.1$	<0.001
Day 2 (°C)	39.5, $s_{\bar{x}} = 0.1$	40.6, $s_{\bar{x}} = 0.1$	<0.001
Day 3 (°C)	39.4, $s_{\bar{x}} = 0.1$	40.6, $s_{\bar{x}} = 0.1$	<0.001
Day 4 (°C)	39.0, $s_{\bar{x}} = 0.1$	40.7, $s_{\bar{x}} = 0.1$	<0.001

[a]Rectal temperature data from day 0 to day 4 were only available from 119 of the 125 animals because 6 animals had died prior to day 5
[b]The least squares mean and standard error calculated from the analysis of variance
[c]The day 0 rectal temperature is the average of the day -1 and day 0 rectal temperatures
The change in rectal temperature from day 0 to day 4 is significantly ($P < 0.05$) different between the experimental groups

organ systems other than the respiratory system should be haemophilosis, not BRD, because *Haemophilus somnus* infection in its various manifestations is the largest cause of mortality in feedlot calves (15–20). However, in the control group of the current study, mortality due to haemophilosis represented 28.6% of all mortality. Thus, the term UF is more appropriate for describing feedlot animals that are febrile with a lack of abnormal clinical signs referable to organ systems other than the respiratory system.

We did not designate animals as suffering from UF unless they had an elevated rectal temperature greater than or equal to 40.5°C for 2 consecutive days. In commercial feedlot production, animals would be treated for UF on the same day as their initial presentation to the hospital facility. In our opinion, the effect of our case definition for UF on the interpretation of our study results is inconsequential by comparison to the substantial variation that exists in the case definition for UF among studies and feedlots. Depending on the assumptions and concepts of illness utilized by each researcher, veterinarian, and animal health manager, the case definition for UF varies immensely. For example, in some feedlots, the case definition for UF is any animal that is presented to the hospital that does not have abnormal clinical signs attributable to organ systems other than the respiratory system. In contrast, the case definition for UF in other feedlots requires an elevated rectal temperature in addition to a lack of abnormal clinical signs attributable to organ systems other than the respiratory system. Similarly, the rectal temperature used to define UF in published studies ranges from 39.5°C to 40.6°C (8,21–26).

Table 6. Culture positive rate (CPR) of transtracheal washes and nasal swabs by experimental group

Source	Pathogen	Florfenicol CPR (%)	Control CPR (%)	*P*-value
Transtracheal wash	PH[a]	7.14	12.20	0.268
	PM[b]	21.43	24.39	0.437
	HS[c]	7.14	4.88	0.805
Nasal swab				
	PH	21.43	17.07	0.789
	PM	15.48	21.95	0.257
	HS	8.33	4.88	0.859

[a]PH is *Pasteurella haemolytica*
[b]PM is *Pasteurella multocida*
[c]HS is *Haemophilus somnus*

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