

CLINICAL EFFICACY OF DANOFLOXACIN IN PNEUMONIC FEEDLOT CATTLE

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Introduction

Bovine respiratory disease is the most common disease associated with recently transported cattle in North American feedlots. Retrospective data collected in 1984 from commercial feedlots in Texas indicate that 83% of total morbidity and 66% of total mortality was attributable to respiratory disease¹. A review of feedlot data from Kansas and Nebraska in 1987 reported similar results with 79% of total morbidity and 67% of total mortality attributed to respiratory disease².

Danofloxacin* is a novel, potent third generation fluoroquinolone which has bactericidal activity against a broad spectrum of bacteria and mycoplasmas of veterinary importance. Minimum inhibitory concentrations expressed as MIC 90's of danofloxacin to a large sampling of common bovine respiratory pathogens Pasteurella haemolytica, P. multocida and Haemophilus sommus have been reported at 0.25, 0.125 and 0.25 µg/ml, respectively³.

This trial was conducted to confirm the therapeutic efficacy of danofloxacin in the treatment of naturally occurring bovine respiratory disease in a research feedlot facility in Texas which maintains management practices typical for the commercial feedlots in the area. Efficacy was assessed based on the reduction in pyrexia, improvement in clinical condition, reduction in number of response failures, prevention of mortality, and the maintenance of normal weight gain.

Materials and Methods

A total of 343 crossbred beef steers and bulls were assembled at sale barns in Alabama and Mississippi and transported approximately 1200 km to a commercial research feedlot in Texas. Upon arrival to the feedlot, animals received a prophylactic regimen consisting of the administration of an anthelmintic (Ivomec®, Merck & Co., Inc.), IBR/PI3/BVD and Clostridial spp vaccines, Vitamins A & D, zeranol implant (Ralgro®, Pitman-Moore, Inc.), and unique identification by eartag. All cattle were observed daily; those animals exhibiting clinical signs of acute pneumonia and a rectal temperature of $\geq 40.0^{\circ}\text{C}$ were individually selected for the trial. Animals in poor condition, chronically ill, or exhibiting signs of other systemic diseases were given appropriate treatment and prohibited from entering the trial.

Once selected for the trial, each animal was randomly allotted to one of two treatment groups receiving either danofloxacin at 1.25 mg/kg or ceftiofur sodium (Naxcel®, UpJohn Co.), at 1.1 mg/kg body weight. Individual weights were recorded, proper doses calculated, and nasopharyngeal swab collected for bacteriological examination prior to the initial treatment. Therapy was administered by deep intramuscular

* ADVOCIN, trademark of Pfizer Inc

injection in the neck for three consecutive days. Twenty-four hours following the third injection, any animals exhibiting clinical signs of pneumonia and/or a rectal temperature of ≥ 39.7 C received two additional daily injections for a total of five consecutive days of therapy.

Clinical examinations were conducted daily during the treatment period and for seven days following the completion of therapy. Each animal was assigned a daily illness score (0=normal and healthy, 1=mildly diseased, 2=moderately diseased, 3=severely diseased, 4=moribund) by an attending veterinarian who was unaware of treatment group identity.

Any animal judged to be severely diseased or moribund as a consequence of recurrence of pneumonia during the seven day post-treatment observation period was removed from the trial to allow for the administration of alternative therapy. Weights were recorded 28 days following initiation of therapy for all animals which did not receive alternative therapy after the initial treatment regimen was completed.

Daily rectal temperature and daily weight gain least square means were analyzed using a general linear model to partition variation. The Fisher's Exact Test was used to examine differences between the danofloxacin and ceftiofur treatment groups for the duration of therapy (three days vs. five days), the proportion of animals successfully responding to therapy, and the proportion of animals removed from the trial as response failures.

Results

A total of 205 animals met the selection criteria for acute pneumonia and were allotted to the trial within five days of arrival to the feedlot. Animals were classified as mildly or moderately diseased prior to initial treatment, with 103 animals treated with danofloxacin and 102 receiving ceftiofur.

Rapid and sustained reductions in pyrexia were recorded for animals in both treatment groups following the initiation of therapy. Pre-treatment mean rectal temperatures of 40.7°C and 40.8°C for danofloxacin- and ceftiofur-treated animals respectively were reduced significantly ($P \leq 0.05$) within 24 hours after initiation of therapy in both treatment groups. Temperatures remained significantly ($P \leq 0.05$) lower than pre-treatment levels throughout the treatment period as evidenced by the mean rectal temperatures recorded for both groups 72 hours following the initiation of therapy (Table 1).

Table 1: Mean Daily Rectal Temperatures During Therapy ($^{\circ}\text{C}$)

| Treatment | Animals | Hours Following Initiation of Therapy | | | |
|--------------|---------|---------------------------------------|-------|-------|-------|
| | | 0 | 24 | 48 | 72 |
| Danofloxacin | 103 | 40.7 | 39.9* | 39.4* | 39.5* |
| Ceftiofur | 102 | 40.8 | 40.0* | 39.6* | 39.4* |

* Within a treatment, means with an asterisk are significantly different from the day 0 mean ($P \leq 0.05$).

Improvement in clinical condition was evident at the completion of therapy in both treatment groups. Within the danofloxacin treatment group, 88% of the animals successfully responded to therapy and were classified as healthy and normal or only mildly diseased. For the animals treated with ceftiofur, 82% were classified as healthy and normal or only mildly diseased 24 hours following the completion of therapy. Due to the broad criteria for extending therapy 2 additional days, the majority of animals in both treatment groups received 5 days of initial therapy (Table 2).

Table 2: Clinical Response to Initial Therapy Assessed 24 Hours Post-Treatment

| Treatment | Animals | Days of Initial Therapy | | % Animals Successfully Responding* |
|--------------|---------|-------------------------|----|------------------------------------|
| | | 3 | 5 | |
| Danofloxacin | 103 | 8 | 95 | 88 |
| Ceftiofur | 102 | 8 | 94 | 82 |

* A successful response was defined as an illness score of 0 (normal and healthy) or 1 (mildly diseased).

During the 7-day post-treatment observation period, the clinical condition deteriorated to severely diseased or moribund as a consequence of recurrence of pneumonia in 19 ceftiofur and 7 danofloxacin-treated animals. The animals which relapsed were removed from the trial. The difference between groups for the number of animals which relapsed was significant ($P \leq 0.05$). No animals in either treatment group died during the treatment or post-treatment observation period (Table 3).

Table 3: Clinical Observations During 7 Day Post-Treatment Period

| Treatment | Animals | Animals Relapsing* | Mortality |
|--------------|---------|--------------------|-----------|
| Danofloxacin | 103 | 7 ^a | 0 |
| Ceftiofur | 102 | 19 ^b | 0 |

* Any animal with an illness score ≥ 3 during the 7-day post-treatment period.

^{ab} Within a column, means not sharing a common letter are significantly different ($P \leq 0.05$)

The mean daily weight gains over a 28-day period for animals which did not receive alternative therapy were 1.27 and 0.95 kg for danofloxacin and ceftiofur treatments, respectively (Table 4). The overall rate of

gain seen in these animals was within the normal range expected for healthy animals during the first few weeks in the feedlot. The difference in weight gains between treatments was statistically significant.

Table 4: Weight Gain

| <u>Treatment</u> | <u>Number of Animals*</u> | <u>Mean Daily Weight Gain (Kg)</u> |
|------------------|---------------------------|------------------------------------|
| Danofloxacin | 83 | 1.27 ^a |
| Ceftiofur | 71 | 0.95 ^b |

^{a,b} Within a column, means not sharing a common letter are significantly different ($P \leq 0.05$)

* Animals which received alternative therapy or died are not included in the analysis.

Minimum inhibitory concentrations (MICs) of danofloxacin against isolates of *P. haemolytica*(60) and *P. multocida*(47) recovered from pre-treatment nasopharyngeal swabs ranged from 0.06 $\mu\text{g/ml}$ to 0.25 $\mu\text{g/ml}$ and 0.015 $\mu\text{g/ml}$ to 0.25 $\mu\text{g/ml}$, respectively. All isolates were inhibited by 1 $\mu\text{g/ml}$ ceftiofur, the lowest concentration tested.

Conclusion

Danofloxacin was highly effective in the treatment and control of naturally occurring bovine respiratory disease when administered by intramuscular injection at 1.25 mg/kg for three or five days. Danofloxacin therapy rapidly reduced pyrexia and improved clinical condition during the treatment period. Twenty-four hours following therapy, 88% of danofloxacin-treated animals had successfully responded to therapy. The restoration of health was also evident in the weight gains recorded over a 28-day period, which were similar to those expected in healthy calves. Therapy with ceftiofur was equally effective, except in its ability to minimize relapses in which danofloxacin was significantly ($P \leq 0.05$) better.

Summary

Danofloxacin, a novel third-generation fluoroquinolone antibacterial, was evaluated in the therapy of acute pneumonic pasteurellosis occurring in newly arrived 184 kg cattle at a commercial research feedlot in Texas. A total of 205 steers and bulls were individually selected upon clinical presentation of acute pneumonia and randomly allotted to receive either danofloxacin (n=103) at 1.25 mg/kg s.i.d. or ceftiofur (n=102) at 1.1 mg/kg s.i.d.. Treatment was administered by intramuscular injection for three consecutive days with the option of two additional days of therapy if necessary. Danofloxacin and ceftiofur rapidly reduced rectal temperatures with significantly ($P \leq 0.001$) lower temperatures recorded 24 hours following allotment and throughout the treatment period compared to pre-treatment values. Clinical condition also improved in both treatment groups with 88% of

the danofloxacin-treated animals and 82% of the ceftiofur-treated animals classified as normal or only slightly ill 24 hours following the final treatment. Therapy with danofloxacin resulted in significantly ($P \leq 0.05$) fewer relapses of pneumonia during the post-treatment observation period when compared with ceftiofur therapy. No mortality was recorded for animals on trial in either treatment group. Mean daily weight gain for danofloxacin- or ceftiofur-treated animals was significantly different between treatments (1.27 kg vs. 0.95 kg). Pasteurella haemolytica (n=60) and P. multocida (n=47) isolated from pre-treatment nasopharyngeal swabs were all sensitive to danofloxacin (MIC ≤ 0.25 $\mu\text{g/ml}$) and to ceftiofur (MIC ≤ 1 $\mu\text{g/ml}$).

Resumen

Danofloxacin, un nuevo antibacteriano perteneciente al grupo de las quinolonas de tercera generacion, fue evaluado en la terapia de la pateuriosis neumonica aguda en bovinos de 184 Kg recién llegados a corrales de engorda para investigacion en Texas. Un total de 205 novillos fueron seleccionados individualmente al presentar signos clinicos de neumonia aguda, y fueron repartidos al azar para ser tratados ya sea con danofloxacin (n=103) a razon de 1.25 mg/Kg una vez al dia, o con ceftiofur (n=102) a razon de 1.1 mg/Kg una vez al dia. Los tratamientos fueron aplicados por inyeccion intramuscular durante tres dias consecutivos con la opcion de 2 dias adicionales de terapia en caso necesario. Danofloxacin y ceftiofur redujeron rapidamente la temperatura rectal, con temperaturas significativamente ($p \leq 0.001$) menores registradas 24 horas despues de la asignacion a los grupos de tratamiento y durante todo el periodo de tratamiento, comparado con los valores pre-tratamiento. El estado clinico tambien mejoro en ambos grupos de tratamiento, siendo clasificados como normales o ligeramente enfermos un 88% de los animales tratados con danofloxacin y un 82% de los tratados con ceftiofur, 24 horas despues de la ultima inyeccion. La terapia con danofloxacin resulto en significativamente ($p \leq 0.05$) menos respuestas fallidas durante el periodo de observacion post-tratamiento en comparacion con la terapia a base de ceftiofur. No se observo ninguna mortalidad entre los animales incluidos en los grupos de tratamiento. La ganancia de peso diaria promedio de los animales tratados con danofloxacin o con ceftiofur fue significativamente diferente (1.27 Kg vs 0.95 Kg). Pasteurella haemolytica (n=60) y P. multocida (n=47) aisladas a partir de hisopos nasofaringeos antes del tratamiento fueron todas sensibles a danofloxacin (MIC ≤ 0.25 $\mu\text{g/ml}$) y a ceftiofur (MIC ≤ 1 $\mu\text{g/ml}$).

Résumé

La danofloxacin, nouvelle fluoroquinolone de troisième génération, a été comparée au ceftiofur dans le traitement de la pneumonie aiguë à pasteurelles chez des bovins de 184 kg récemment arrivés dans une unité expérimentale d'élevage intensif au Texas. 205 mâles castrés et non castrés présentant des signes cliniques de pneumonie aiguë furent sélectionnés et répartis au hasard en 2 groupes traités soit par la danofloxacin (n= 103, 1,25 mg/kg/jour), soit par le ceftiofur (n=102, 1,1 mg/kg/jour). Les traitements furent administrés par voie intra-musculaire pendant 3 ou 5 jours consécutifs suivant l'amélioration des symptômes cliniques.

Les deux traitements ont entraîné une baisse rapide des températures rectales. Les températures observées 24 heures après l'allotement et

pendant toute la durée de la thérapie se révélèrent significativement ($p \leq 0,001$) inférieures à celles observées avant traitement. De plus, l'état clinique des animaux s'améliora dans les deux groupes, 88% des animaux traités par la danofloxacin et 82% de ceux traités par le ceftiofur furent considérés comme guéris ou légèrement malades 24 heures après le dernier traitement.

Cependant, en comparaison avec le ceftiofur, le groupe traité par la danofloxacin fut caractérisé par significativement ($p \leq 0,05$) moins de rechutes de pneumonie au cours de la période d'observation. Aucune mortalité ne fut enregistrée dans les deux groupes.

Une différence significative de gain moyen quotidien des animaux ayant terminé l'essai a pu être établie entre les deux groupes (1,27 kg et 0,95 kg pour la danofloxacin et le ceftiofur respectivement).

Pasteurella haemolytica (60 souches) et Pasteurella multocida (47 souches), isolés à partir d'écouvillons naso-pharyngés pris avant l'initiation des traitements, se révélèrent sensibles à la danofloxacin ($\text{CMI} \leq 0,25 \mu\text{g/ml}$) et au ceftiofur ($\text{CMI} \leq 1 \mu\text{g/ml}$).

References

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