THE EVALUATION OF DANOFLOXACIN IN THE THERAPY OF PNEUMONIA ASSOCIATED WITH PASTEURELLA SPECIES IN YOUNG CALVES - A SUMMARY

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INTRODUCTION

Acute pneumonia is an economically important disease afflicting young cattle world-wide. The disease develops as a complex interaction and the aetiology of any outbreak is often multi-factorial (1). *Pasteurella spp.* are the most important bacteria involved causing fibrinous bronchopneumonia (2, 3), but more frequently they increase the severity of lung lesions inflicted by viruses and/or mycoplasmas. Transport, housing and mixing of animals are management factors contributing to outbreaks of acute pneumonia. This paper summarizes the results of seven studies conducted in Europe in which the efficacy of the fluoroquinolone antimicrobial danofloxacin* against naturally occurring outbreaks of acute pneumonia in calves was evaluated in comparison with trimethoprim/sulpha.

MATERIALS AND METHODS

Animals and Management

Seven studies were conducted on farms located in Germany (4), Belgium (1), Italy (1) and Netherlands (1). Outbreaks of pneumonia associated with infection by *Pasteurella spp.* had occurred regularly on these farms. The calves were purchased when approximately one week of age and transported to the farms where they were housed. All calves were fed milk replacer twice daily. Prophylactic treatments and supportive therapy were not allowed prior to or during the study period.

Experimental design

A similar experimental procedure was applied in all seven studies. On arrival at the farm the calves were individually identified and examined daily for evidence of respiratory disease. Treatment was initiated only when specific diagnostic criteria were met. These were clinical signs of acute pneumonia together with a rectal temperature equal to or greater than 40.0^0 C. Upon meeting the criteria, animals were randomly allocated to one of the two treatment groups, weighed and nasopharyngeal swabs were collected for bacteriological examination.

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Calves were treated with danofloxacin at 1.25 mg/kg bodyweight or trimethoprim/sulpha administered at the label recommended dose. In six studies the dose level of trimethoprim/sulpha was 4/20 mg/kg and in the Belgian study it was 2,7/13.3 mg/kg. Treatments were administered by intramuscular injection into the neck and all animals were treated once daily for three consecutive days. If the rectal temperature of a calf was equal to or greater than 39.5^0 C and/or clinical signs of pneumonia were still present on clinical examination 24 hours after the third injection, treatment was continued for a further two days.

Detailed daily clinical observations were made during treatment and for five days after treatment ceased. At each examination the rectal temperature was recorded, the rate and character of respiration assessed and the presence of other clinical signs recorded. On the basis of these observations an overall illness score of zero (normal), one (mildly affected), two (moderately affected) three (severly affected) or four (moribund) was assigned to each animal. Parameters were predefined and were applied by the investigators as consistently as possible within and between trials.

Bacteriological Examination

Isolation and identification of *Pasteurella spp.* and other significant bacterial respiratory pathogens were carried out. Minimum Inhibitory Concentrations (MICs) of danofloxacin and trimethoprim/sulpha drug against *Pasteurella spp.* were determined using a micro-adaptation of the broth dilution method (Sensitire Susceptibility System, Sensititre Ltd., Crawley, U.K.).

Data analysis

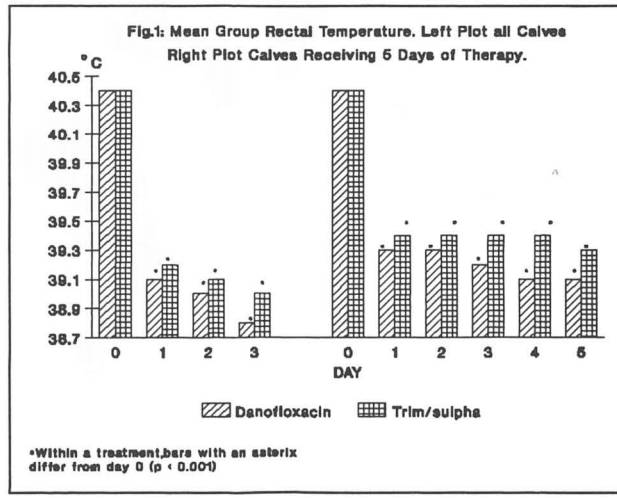
Daily rectal temperatures were statistically analyzed using a split-plot Anova model. Differences in least squared means between treatment groups within a particular day and between days on test within a treatment group were analyzed.

Clinical response during therapy and the five day post-treatment period was assessed by determining on each day the population of animals whose clinical condition was improved compared to pre-treatment (i.e. whose illness score on a particular treatment day was less than its illness score on the day of initial treatment). A variable derived from both temperature and illness score was used to obtain a retrospective assessment of individual animal response to therapy 24 hours after completion of treatment. The definition of this variable was based on stringent clinical criteria, which required both control of pyrexia (rectal temperature $<39.5^0$C) and moderation of primary clinical signs (illness score of ≤ 1) for an animal to be classified as responding successfully. The Fisher's Exact Test (two-tailed) was used to examine the differences between treatments for these response variables and for duration of therapy.

RESULTS

Clinical observations were made on 170 calves receiving danofloxacin and on 174 calves receiving trimethoprim/sulpha. The clinical nature of the respiratory disease outbreaks on the seven farms was similar and was considered as moderate in severity. Three animals died in the trimethoprim/sulpha treatment group. Post-mortem examination confirmed that two calves died of pneumonia. The third calf was euthanized as it did not adjust to drink the milk replacer.

Within 24 hours of initiation of treatment there was a rapid and significant ($p<0.001$) fall in rectal temperature in both treatment groups (Figure 1). Twenty-four hours after the third injection 91 (52 percent) of the trimethoprim/sulpha-treated calves met the criteria for two additional days therapy, compared with 71 (42 percent) of the danofloxacin-treated calves (Table 1). Comparison of the mean rectal temperatures demonstrate that the rectal temperatures of danofloxacin-treated calves were consistently lower than those of the calves treated with trimethoprim/sulpha throughout the treatment period although the differences were not statistically significant (Fig. 1).



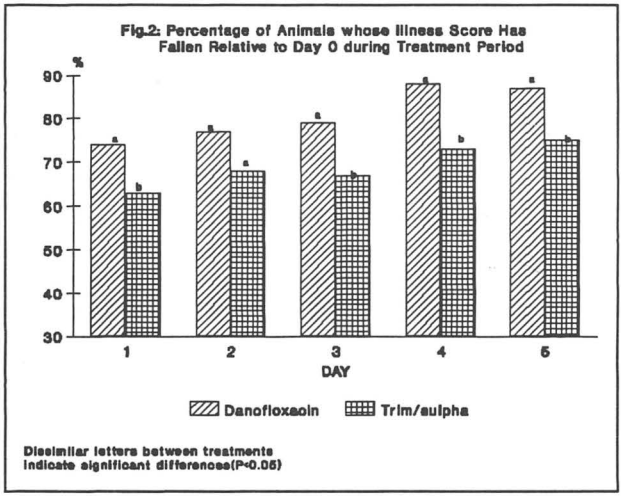
The clinical condition of treated calves improved in parallel with the reduction of pyrexia in a similar way among treatment groups in all studies. The percentage of calves whose illness score had fallen relative to pre-treatment is shown in figure 2. Twenty-four hours after treatment initiation 74 percent of the danofloxacin calves had improved compared to only 63 percent in the trimethoprim/sulpha group ($p\leq0.05$). This difference between groups continued during the treatment period and was significant ($p\leq0.05$) on four out of five days.

Applying the response variable which combines both temperature and illness score, 145 animals (85 percent) in the danofloxacin group and 110 animals (63 percent) in the trimethoprim/sulpha group were classified as successfully responding 24 hours after cessation of treatment. The difference between groups is statistically significant ($p\leq0.05$). The superior response to danofloxacin was achieved with fewer days of therapy (Table 1).

Table 1 - Duration of therapy and clinical response

Treatment	No. of Animals	3 Days Therapy	5 Days Therapy	No. Responding
Danofloxacin	170	99(58)	71(42)	145(85)[a]
Trim./sulpha	174	83(48)	91(52)	110(63)[b]

( ) Percentage
[a,b]p ≤0.05



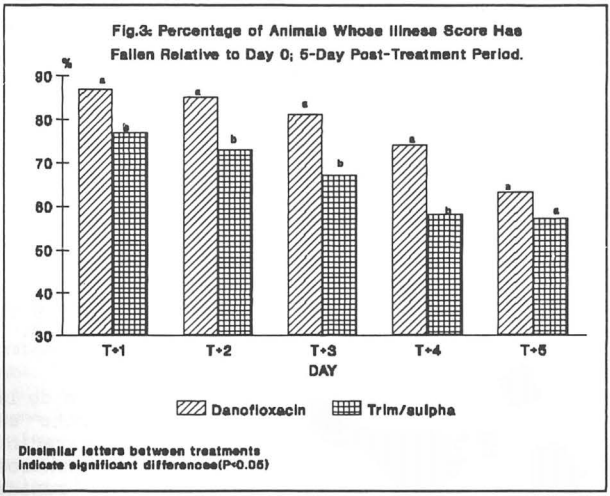
Applying the response variable on the subset of animals that entered the study as moderately and severely ill (illness score of two or three) 80 percent of animals in the danofloxacin group responded successfully compared to 57 percent in the trimethoprim/sulpha group. The difference is significant (p≤0.05) (Table 2).

Table 2 - Clinical response to therapy 24 hours post-treatment. Moderately and severly ill animals.

Treatment	No. of Animals	No. of Animals Responding	No. of Animals 3-Day Therapy
Danofloxacin	115	92(80)[a]	59(51)
Trim./sulpha	108	62(57)[b]	47(44)

( ) Percentage
[a,b]p ≤0.05

During the five-days post-treatment observation period the percentage of calves whose illness score had fallen relative to pre-treatment was higher for the danofloxacin group than for the trimethoprim/sulpha group. The difference between groups was statistically significant (p≤0.05) on all days except day 5 (Fig. 3).



Bacteriological Observations

Overall 165 isolates of *Pasteurella haemolytica* and 127 isolates of *Pasteurella multocida* were recovered from pre-treatment nasopharyngeal swabs. These isolates demonstrated high susceptibility to danofloxacin with an MIC_{90} value of 0.25 mcg/ml for both *P. haemolytica* and *P. multocida* (Table 3). The MIC_{90} for trimethoprim was 2.0 mcg/ml for *P. haemolytica* and 4.0 mcg/ml for *P. multocida*; although the MIC_{50} for both pathogens were ≤0.25 mcg/ml.

Table 3

Minimum Inhibitory Concentration (MIC) Against Pasteurella spp. (μg/ml)

		Trim./Sulpha				Danofloxacin			
Organism	No. of Isolates	Min.	Max	MIC_{50}	MIC_{90}	Min.	Max	MIC_{50}	MIC_{90}
P.hemolytica	165	≤.25	16	≤.25	2	.015	2	.125	.25
P.multocida	127	≤.25	16	≤.25	4	.008	4	.03	.25

DISCUSSION AND CONCLUSION

The results of these field studies demonstrate that danofloxacin was highly effective in the treatment of calf respiratory disease associated with *Pasteurella* species. In addition, the results achieved with danofloxacin were significantly better than those obtained with trimethoprim/sulpha. Trimethoprim/sulpha was selected as the comparator drug in these studies because it is considered to be one of the most effective antibacterials for the treatment of bacterial respiratory disease. The vast majority of *Pasteurella spp.* isolated in these studies were highly susceptible to danofloxacin. A low incidence of resistance to trimethoprim/sulpha was recorded. However, it is unlikely that the difference in efficacy between the two drugs can

be explained on the basis of bacterial resistance. It is more likely that the superior efficacy of danofloxacin in these studies is attributable to its mode of action, potency and pharmacokinetics (4,5,6,7).

SUMMARY

The antimicrobial danofloxacin was evaluated in the therapy of pneumonic pasteurellosis in intensively reared, milk-fed calves on seven farms in Europe in comparison with trimethoprim/sulpha. Danofloxacin was adminstered to 170 calves and trimethoprim/sulpha to 174. Both drugs caused a rapid reduction in group mean rectal temperature and improved clinical condition in the majority of the calves. The treatment with danofloxacin resulted in fewer treatment days, better control of pyrexia, a significantly higher clinical response rate and better resolution of clincial signs.

RESUMEN

El antimicrobiano danofloxacin fue evaluado en la terapia de la pasteurelosis neumonica en terneros alimentados con leche en instalaciones intensivas en siete granjas de Europa, en comparacion con trimetoprim/sulfa. Danofloxacin fue administrado a 170 terneros y trimetoprim/sulfa a 174. Ambas drogas causaron una rapida reduccion en la temperatura rectal promedio del grupo y mejoraron la condicion clinica en la mayoria de los animales. El comportamiento de danofloxacin resulto en menos dias de tratamiento, mejor control de la pirexia, una tasa de respuesta clinica significativamente mejor y una mejor resolucion de los signos clinicos.

RESUMÉ

L'antimicrobien danofloxacine a été comparé á l'association triméthoprime/sulfa dans le traitement de la pasteurellose pulmonaire chez des veaux en élevage intensif, nourris au lait, dans sept fermes en Europe. La danofloxacine fut administrée á 170 veaux et le triméthoprime/sulfa á 174. Les deux produits ont entrainé une réduction rapide de la température rectale moyenne du groupe et ont provoqué une amélioration de la condition clinique chez la majorité des veaux. La performance de la danofloxacine s'est traduite par une diminution des jours de traitement, un meilleur contrôle de la pyrexie, un taux de réponse clinique significativement plus élevé et une meilleure résolution des signes cliniques.

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