THE EFFICACY OF DANOFLOXACIN IN THE THERAPY OF ACUTE BACTERIAL PNEUMONIA IN HOUSED BEEF CATTLE - A SUMMARY

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INTRODUCTION

Danofloxacin* is an antimicrobial of the fluoroquinolone class, and has shown potent *in vitro* activity against the major bacterial pathogens involved in respiratory disease, *Pasteurella haemolytica* and *Pasteurella multocida*(1). Pharmacokinetic studies with danofloxacin in cattle have demonstrated an attractive profile. The drug is rapidly absorbed and distributed to respiratory tract tissues and secretions following intramuscular or subcutaneous administration (2,3). This paper summarizes the results of 11 studies in beef cattle conducted in Europe. The efficacy of danofloxacin against naturally occurring outbreaks of acute pneumonia was evaluated in comparison with oxytetracycline and trimethoprim/sulpha.

MATERIALS AND METHODS

Animals and Management

Eleven trials were conducted on different commercial farms located in France (4), Italy (3), Germany (2), Ireland (1) and Spain (1). Animals between six and nine months of age were transported to the farms for intensive fattening indoors. All farms had a history of outbreaks of acute pneumonia associated with *Pasteurella* infection occurring shortly after arrival of cattle. The animals were fed according to farm practice and water was supplied *ad libitum*. Prophylactic treatments and supportive therapy were not allowed prior to or during the study period.

Experimental Procedure

A similar experimental procedure was applied in all studies. After arrival the animals were individually identified and subjected to daily examinations. Treatment was initiated when clinical signs of acute pneumonia were present together with a rectal temperature $\geq 40.0^{0}$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. Treatment with danofloxacin (1.25 mg/kg) was compared with oxytetracycline (10mg/kg; France, Ireland) and trimetroprim/sulpha (4/20 mg/kg; Germany, 2.7/13.3; Italy, Spain).

*ADVOCIN, trademark of Pfizer Inc.

All dose levels were according to local label recommendations. Treatments were administered by intramuscular injection into the neck and all animals were treated once daily for three consecutive days. If, on clinical examination 24 hours after the third injection the rectal temperature was ≥39.5°C and/or pronounced clinical signs of pneumonia were still evident, treatment was continued for a further two days. Clinical examinations were performed prior to each treatment and for the five days following completion of treatment. 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 diseased), two (moderately diseased), three (severely diseased) 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. Animals with an illness score of three or four during the five days post-treatment observation period were removed from the trial.

Bacteriological Examination

Isolation and identification of *Pasteurella* spp. and other significant bacterial respiratory pathogens were carried out using standard techniques. Minimum Inhibitory Concentrations (MICs) of danofloxacin and the reference drug against *Pasteurella* spp. were determined using a micro-adaptation of the broth dilution method (Sensititre 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 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

The clinical nature of the respiratory disease outbreaks on the eleven farms was similar and typical of transit fever pneumonia of mild to moderate severity. Five hundred and ninety-nine cattle met the diagnostic criteria for inclusion in the trial. Three hundred animals received danofloxacin and 299 were administered one of the reference drugs (Table 1).

Four animals died during the course of the trials. Three occurred on one trial site in animals treated with danofloxacin. The diagnosis was pneumonia and serology confirmed the presence of viral disease on this farm. The fourth was treated with oxytetracycline and the autopsy confirmed the presence of pneumonia.

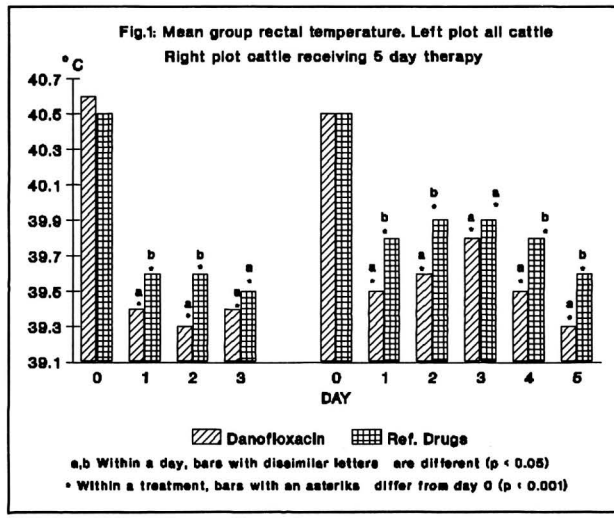
Sixty-three percent of the animals (187 cattle) treated with the reference drugs required five days therapy. The corresponding figure in the danofloxacin group was 34 percent (103 cattle). The difference in duration of therapy between the treatment groups was statistically significant ($p \leq 0.05$) (Table 1).

Table 1 - Duration of Therapy and Clinical Response
Assessed 24 h Post-Treatment

Treatment (n)	3 Days Therapy(%)	5 Days Therapy(%)	No. of Animals Responding (%)
Danofloxacin (300)	197(66)[a]	103(34)[a]	256(85)[a]
Reference Drug (299)	112(37)[b]	187(63)[b]	163(55)[b]
Danofloxacin (165)	102(62)[a]	63(38)[a]	149(90)[a]
Oxytetracycline (159)	47(30)[b]	112(70)[b]	78(49)[b]
Danofloxacin (135)	95(70)[a]	40(30)[a]	107(79)[a]
Trim./Sulpha (140)	65(46)[b]	75(54)[b]	85(61)[b]

[a,b] $p \leq 0.05$

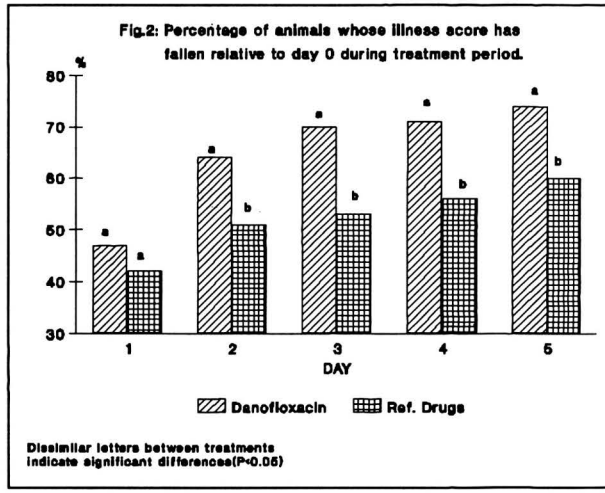
The effect of therapy on pyrexia is illustrated in Figure 1. Prior to treatment the group mean rectal temperatures were similar in both treatment groups. A rapid and significant fall in group mean rectal temperature occurred in both groups (≤ 0.001), and remained significantly lower than before treatment for the entire treatment period. The group mean rectal temperature of the cattle treated with danofloxacin was significantly lower ($p \leq 0.05$) on all days of therapy, except day three, than for cattle treated with the reference drugs. The group mean rectal temperature and the reductions



of pyrexia for the subset of animal treated five days followed the same pattern as described for all cattle over three days (Fig. 1).

The clinical condition of treated animals improved in parallel with the reduction of pyrexia in a similar way among treatment groups in all studies. The clinical recovery is shown in Figure 2 as the percentage of cattle having an improved illness score compared to pre-treatment. Twenty four hours after initiation of therapy 47 percent of cattle treated with danofloxacin had clinically improved compared to 42 percent in the control group. During the remaining part of the treatment period the difference in clinical improvement was statistically significant ($p \leq 0.05$). On day of test five, 74 percent in the danofloxacin treated group had improved clinically compared to 60 percent in the control group (Fig. 2).

Applying the response variable which combines both temperature and illness score, 256 animals (85 percent) in the danofloxacin group and 163 animals in the reference group (55 percent) were classified as successfully responding 24 hours after cessation of treatment (Table 1). The difference between groups is statistically significant ($p \leq 0.05$).



When the response variable described above is applied on the subset of animals that entered the study with an illness score of 2 or 3, significantly ($p \leq 0.05$) more animals in the danofloxacin group (77%) responded successfully compared with the control group (53%), with significantly fewer days of therapy ($p \leq 0.05$) (Table 2).

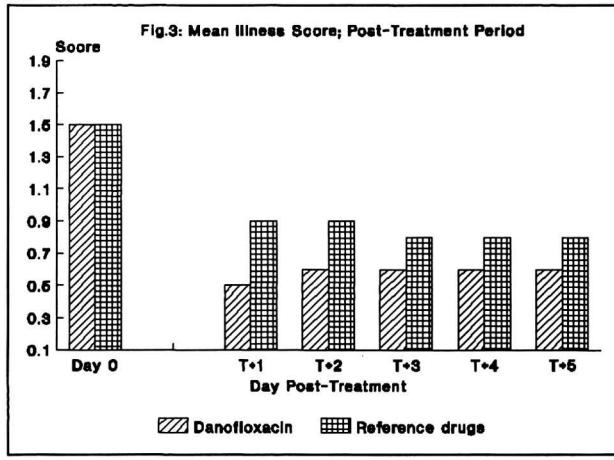
Table 2 - Clinical response to therapy assessed 24 hours post-treatment. Moderately and severly ill animals.

Treatment	No. of Animals	No. of Animals Responding	No. of Animals 3-Days Therapy
Danofloxacin	124	96(77)[a]	81(65)[a]
Reference Drugs	116	61(53)[b]	54(47)[b]

( ) percentage
[a,b] $p \leq 0.05$

Clinical progress during the five days observation period is

demonstrated in Figure 3. The mean illness score pre-treatment was 1.5 in both the danofloxacin group and in the control group. Twenty-four hours after last treatment the mean illness score in the danofloxacin group was reduced to 0.5, but was considerably higher at 0.9 in the control group. The difference in mean illness score between treatment groups was also present for the remaining part of the post-treatment observation period. At the end of the observation period 65 percent of danofloxacin treated cattle had an illness score of zero compared to 56 percent in the control group. Ten percent of control animals had been culled, euthanized or removed from the trial with an illness score of three or four, compared to only six percent in the danofloxacin group.



Bacteriological Observations

The isolates of *P.haemloytica* and *P.multocida* were all highly sensitive to danofloxacin, and the majority of strains were also sensitive to trimethoprim/sulpha. Most *P.multocida* were sensitive to oxytetracycline, but a certain proportion of *P.haemolytica* isolates were not susceptible to oxytetracyline (Table 3).

Table 3 - Minimum Inhibitory Concentrations (μg/ml)

	P.haemolytica				P.multocida			
Drug	No. of isolates	Min.	Max.	MIC_{50}	No of. isolates	Min.	Max.	MIC_{50}
Danofloxacin	129	≤0.008	1	0.06	44	≤0.008	2	0.015
Oxytetracycline	129	≤0.5	>64	1	44	≤0.5	>64	≤0.5
Danofloxacin	47	≤0.008	0.125	0.06	26	≤0.008	0.03	0.015
Trim./Sulpha	47	≤0.25	0.5	≤0.25	26	≤0.25	8	≤0.25

DISCUSSION AND CONCLUSION

Danofloxacin was highly efficacious in the treatment of respiratory disease in these studies and the results achieved were superior to those obtained with the reference drugs. The vast majority of the *Pasteurella spp.* isolated in these studies were highly susceptible

to danofloxacin and trimethoprim/sulpha. Some resistance to oxytetracycline was recorded. The superior efficacy of danofloxacin is probably related to its inherent higher potency and superior pharmacokinetic properties, as the relatively low incidence of bacterial resistance to oxytetracycline is unlikely to explain the difference in efficacy between the two drugs. Therapy with danofloxacin resulted in fewer treatment days, more rapid and complete control of pyrexia, a significantly higher clinical response rate and resolution of clinical signs.

SUMMARY The therapeutic efficacy of danofloxacin was evaluated in acutely pneumonic beef cattle in comparison with oxytetracycline and trimethoprim/sulpha on eleven farms in Europe. Three hundred cattle were treated with danofloxacin and 299 with one of the reference drugs. Both treatment regimens resulted in a rapid reduction of mean rectal temperatures and improved the clinical condition in the majority of the animals. Therapy with danofloxacin resulted in significantly fewer treatment days, a significantly higher response rate, better reduction of pyrexia and fewer cattle requiring re-treatment.

RESUMEN La eficacia terapeutica de danofloxacin fue evaluada en bovinos de carne con neumonia aguda en comparacion con oxitetraciclina y trimetoprim/sulfas en siete granjas en Europa. Trescientos bovinos fueron tratados con danofloxacin y 299 con alguna de las drogas de referencia. Ambos regimenes de tratamiento resultaron en una rapida reduccion de la temperatura rectal promedio y mejoraron la condicion clinica en la mayoria de los animales. La terapia con danofloxacin resulto en significativamente menos dias de tratamiento, una tasa mas alta de respuesta, una mejor reduccion de la pirexia y menos bovinos requirieron un retratamiento.

RESUMÉ L'efficacité therapeutique de la danofloxacine a été comparée á celle de l'oxytétracycline et de l'association triméthoprime/sulfa chez des bovins á viande atteints de pneumonie aigue dans onze fermes en Europe. Trois cent bovins ont été traités avec la danofloxacine et 299 avec l'une des médications de référence. Les deux régimes thérapeutiques ont entrainé une réduction rapide des temperatures rectales moyennes et ont provoqué une amélioration de la condition clinique chez la majorité des animaux. La danofloxacine a nécessité un nombre moins important de jours de traitement, tout en entrainant un taux de réponse plus élevé, une meilleure réduction de la pyrexie et moins d'animaux nécessitant un traitement ultérieur.

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