Clinical Efficacy of Enrofloxacin Against Bovine Respiratory Disease Comparing Different Treatment Regimens

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Abstract

Enrofloxacin is being successfully used for the treatment of Bovine Respiratory Disease in many countries. The established treatment regimen is a daily injection for 3 to 5 days with a dose range from 2.5 - 5.0 mg/kg/b.w. Since the discovery of the compound it has been the subject of intensive clinical research worldwide. One of the predominant findings was that a single treatment with an elevated dosage of 7.5 - 12.5 mg/kg/b.w. demonstrates excellent clinical efficacy under feedlot conditions. The current report presents the results of several clinical field trials which were conducted in the USA and Europe during the last years in order to compare the clinical efficacy of the daily and single treatment regimens. The studies were carried out under varied housing and weather conditions.

The results demonstrate the equivalency of both treatment regimens. Consequently, the usage of enrofloxacin enables veterinarians to utilize their experience and medical expertise to design either a daily or a single treatment regimen according to the specific infection and management situation.

Introduction

The fluoroquinolone enrofloxacin, active ingredient of Baytril®, has been shown in several previous studies to be a highly effective antimicrobial drug for the treatment of Bovine Respiratory Disease (BRD) (1,2). The established and in most countries registered dose range is 2.5 - 5.0 mg/kg given once daily for 3 to 5 days.

Since the discovery of the fluoroquinolones, they have been the subject of intensive research worldwide. One of the predominant findings was that the peak concentration (C_{max}) and the area under the curve (AUC), but not the time above the minimum inhibitory concentration (MIC), are the most important pharmacokinetic parameter to predict the clinical efficacy (3,4). This led to the idea that a single elevated dose of 7.5 - 12.5 mg/kg of enrofloxacin might be effective for the treatment of BRD (5).

If a single elevated dose of enrofloxacin would show comparable results to the established daily treatment regimen it would enable veterinarians to use their experience and medical expertise to design either a daily or single treatment regimen according to the specific infection and management situation.

Clinical field trials were conducted in the USA and Europe during the last several years to compare the clinical efficacy of both treatment regimens.

Materials and methods

Studies A, B and C were conducted in the USA. Male and female commercial crossbred calves, 4 months of age or older were used. The animals were gathered from various commercial feeder calf sources. They varied in size and age and were representative of a feedlot population. The calves were transported by truck to the feedlot and commingled in large pens. Standard processing such as vaccination, castration, deworming, ear tagging and administration of growth implants was performed on all calves according to local feedlot practices. In all three studies virtually the same protocol was followed.

Two investigators were required to conduct the study enabling blinding of the disease-scoring investi-

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gator from the treatments. All animals were observed daily beginning on the day of arrival for clinical signs consistent with BRD.

After meeting a defined set of entrance criteria, animals were randomly assigned to either a treatment group or to the placebo control group. The clinical parameters attitude, appetite, respiration, body temperature and mortality were measured or scored daily throughout the study period. Treatment success was defined as meeting a certain set of criteria for two consecutive days either on day 4 and 5 or 5 and 6.

Study A was a single location (California) trial including 48 animals of which 36 animals received the test drug (12 animals received 2.5 mg/kg for three days, 12 animals received a single dose of 7.5 mg/kg and 12 animals received a single dose of 15 mg/kg) and 12 animals served as negative controls. All calves were necropsied on day 15. The total percent lung diseased was determined by adding the proportion of each lobe affected, weighted by the estimated total proportion that each lobe occupies of the total lung.

Study B and C were multicenter studies conducted in different geographical areas of the USA. At each study site about 100 calves were assigned to the treatment group and about 50 calves to the negative control group.

In study B, three locations evaluated the clinical efficacy of a 2.5 mg/kg dose and one site evaluated a 5.0 mg/kg dose administered for three to five days. The study duration was 28 days.

In study C, three locations evaluated the clinical efficacy of a single 7.5 mg/kg dose and one site evaluated a single 12.5 mg/kg dose. The study duration for this trial was 10 days.

Study D was a field efficacy trial which was carried out on commercial beef farms in East Central Scotland. The four included farms that were selected because they had experienced high rates of BRD infections in previous years. Large numbers of highly susceptible cattle were housed together in poorly-designed buildings during early winter when large fluctuations in environmental conditions were commonly experienced. The 164 cattle included in this study were predominantly either Charolais, Simmental or Limousin crossbred female or male beef calves 3 to 9 months of age.

When three or more calves on one of the farms showed clinical signs of BRD all the calves in that group were examined by the veterinarian. Calves which had a rectal temperature greater than 39.6°C were treated either with a daily injection of 2.5 mg/kg for three days or a single injection of 7.5 mg/kg.

The investigation and observation period extended from the initial treatment for fourteen days. The rectal temperature was recorded on days 1, 2, 3 and 7 of the trial. If the rectal temperature of the calves decreased below 39.6°C by the third day after treatment, but subsequently became elevated such that the original admission criteria were met, the calf was retreated.

The calves in all studies were not given antimicrobial prevention before being treated with the test drug. No antibacterial feed additives were allowed in the ration. The calves had ad libitum access to a standard basal ration and water. Baytril®injectable solution was administered subcutaneously in the neck on all study sites. The formulation contained 10% enrofloxacin with arginine.

Results

The results of study A are presented in Table 1. The negative control group had more mortalities, lower treatment success rates as well as higher pulmonic lung scores than the treated groups. No clinical difference was detected among the three treated groups.

Table 1. Results of study A

Group [mg/kg]	N	Mort.	Success	Relapse	% Lung Consol.
Contr.	12	4	0	0	38
2.5 x 3 days	12	0	7	2	14
7.5 x 1 day	12	0	7	1	16
15.0 x 1 day	12	0	8	4	14

The mortality, treatment success rates and relapses for study B and C are presented in Table 2 and 3. The clinical outbreaks of BRD from which the cattle in study B were selected was typical of a moderately severe outbreak. At the Colorado site, harsh weather conditions contributed to the clinical symptoms of the infection. In study C, the infections were more severe at each location. The severity at the Colorado and Texas location can be attributed to a Bovine Virus Diarrhea (BVD) outbreak during the study.

In study B, 398 animals entered the study and received either a dose of 2.5 mg/kg or 5.0 mg/kg. Based on criteria established prior to study initiation 303 (76%) were scored as treatment successes. Of the 199 animals entering the study and assigned to the negative control group, 23 (12%) died during the study. None of the treated animals died.

Of the 406 animals assigned to study C and receiving either 7.5 mg/kg or 12.5 mg/kg , 301 (74%) exhibited treatment successes and 10 (2%) died. In contrast, from the 204 animals assigned to the negative control group, 62 (30%) died during the study attesting to the severity of the disease outbreaks.

The results of study D are presented in Table 4. The mean rectal temperature of calves admitted to the

Table 2. Results of study B

Site	Group [mg/kg]	N	Mort. (%)	Success (%)	Relapse (%)
Calif.	Contr.	50	5 (10)	3 (6)	1 (33)
	2.5	100	0 (0)	80 (80)	17 (21)
Idaho	Contr.	49	8 (16)	17 (35)	0 (0)
	2.5	98	0 (0)	91 (93)	3 (3)
Neb.	Contr.	50	1 (2)	15 (30)	0 (0)
	2.5	100	0 (0)	75 (75)	5 (7)
Colo.	Contr.	50	9 (18)	12 (24)	2 (17)
	5.0	100	0 (0)	57 (57)	6 (11)
Over-all	Contr.	199	23 (12)	47 (24)	3 (6)
	Treat.	398	0 (0)	303 (76)	31 (10)

Table 3. Results of study C

Site	Group [mg/kg]	N	Mort. (%)	Success (%)	Relapse (%)
Calif.	Contr.	52	22 (42)	1 (2)	0 (0)
	7.5	101	2 (2)	73 (73)	3 (4)
Colo.	Contr.	51	16 (31)	7 (14)	1 (14)
	7.5	102	7 (7)	69 (68)	9 (13)
Tex.	Contr.	51	18 (35)	6 (12)	0 (0)
	7.5	101	0 (0)	69 (68)	5 (7)
Neb.	Contr.	50	6 (12)	7 (14)	0 (0)
	12.5	102	1 (1)	90 (88)	7 (8)
Over-all	Contr.	204	62 (30)	21 (10)	1 (5)
	Treat.	406	10 (2)	301 (74)	24 (8)

study exceeded 40.0°C for both treatment regimens. After 24 hours there was a reduction in rectal temperatures to 39.3°C in the three day treatment group and 39.2°C in the single treatment group. Rectal temperatures remained relatively stable in both groups for the rest of the study.

Retreatment rates were 26% for the multiple day dosing regimen and 20% for the single day regimen. Clinically there was no significant difference between the two groups.

In all studies no injection site pain or treatment related reactions were noted by any of the investigators.

Discussion

The three studies conducted in the USA followed virtually the same protocol allowing results to be compared. In study A the % lung consolidation of the necropsied animals was analyzed in addition to the clinical response. No difference could be observed between the treatment groups for any of the measured parameters. This study established the single elevated dose as equivalent to the daily injection regimen. It also suggested that increasing the dose to 15 mg/kg does not improve the results. In study B and C, the severity of infection varied between the studies and locations. This was attributed to the different geographical areas, housing and weather conditions. At the Colorado and Texas sites in study C a BVD virus infection contributed to the severity of the infection and possibly affected the efficacy. Thus the lower treatment success rate of these two locations (68%) versus the Nebraska study (88%) is difficult to compare. The same is true for study B, where a lower success rate at the Colorado site (57%) was likely the result of unusually harsh weather conditions during the study.

Table 4. Results of study D

Group [mg/kg]	N	Temp. on Day 1	2	3	7	Retreat. (%)
2.5 x 3 days	69	40.1	39.3	39.3	39.2	18 (26)
7.5 x 1 day	95	40.2	39.2	39.3	39.1	19 (20)

From the overall mortality rate in the control group in both multicentre studies it can be generally stated that the infection in study C (mortality rate 30%) was more severe than in study B (mortality rate 12%). In spite of this the treatment success and relapse rates were similar for the two studies.

In contrast to the USA studies no pyrexic animal remained untreated in the trial conducted in Scotland. Thus spontaneous recovery could have been obscured by the treatment regimens.

Although the protocol and the circumstances of the study were quite different from studies in the USA the results provide evidence for the clinical efficacy of both treatment regimens.

The body temperature at the beginning and during the course of the study was almost identical for both treatment groups. Within the first 24 hours after treatment, there was a marked reduction in rectal temperatures, but only small reductions thereafter. The reason for the antibiotic retreatment rate of 20% for the single treatment and 26% for the three consecutive day treatment resulted primarily from the strict protocol definition for retreatment based upon recurrence of pyrexia greater than 39.6°C. Reinfection and latent respiratory tract infection may also have contributed to the results.

It can be concluded from the results of these studies that a single elevated dose of 7.5 mg/kg or 12.5 mg/kg enrofloxacin provides comparable results to a daily treatment regimen of 2.5 mg/kg or 5 mg/kg for three to five days. Consequently veterinarians can utilize this flexibility to apply their experience and medical expertise to design treatment regimens according to the specific infection and management situation.

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CVM UPDATE

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Sentencing in Animal Drug Smuggling Case

On June 12, 1998, in the U.S. District Court, Northern District of Iowa, Dennis G. Doidge, Lions Head, Ontario, Canada, was sentenced to 15 months in prison and fined $100,000 for conspiring to smuggle illegal animal drugs into the United States from Canada.

Several years ago, FDA became aware that unapproved animal drugs (bulk drugs) were being illegally distributed to veterinarians and medicated premix manufacturers who did not hold approved new animal drug applications. No information was available for FDA to evaluate those bulk drugs' safety and effectiveness for their intended use, and nothing was known about the conditions under which they were manufactured. Therefore, FDA had serious concerns about the potential for these drugs to cause unsafe residues in food animals.

Joint investigations by FDA and the Department of Justice revealed a nationwide, loosely knit network of persons involved in the black market trade of these bulk animal drugs. Mr. Doidge, a Canadian citizen, pled guilty to conspiring along with two Canadians and several Americans to smuggle more than $1.2 million worth of unapproved animal drugs into the United States between 1983 and 1988. Nearly all of his confederates were brought to justice in the late 1980s or early 1990s. Mr. Doidge was indicted by a Federal grand jury on October 20, 1988, but he was able to evade prosecution by remaining outside of the United States. He was arrested while attempting to visit Las Vegas, Nevada, on vacation on November 30, 1997.

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