Effects of Arrival Medication with Gamithromycin on Bovine Respiratory Disease in Feedlot Cattle in Italy*

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KEY WORDS: gamithromycin, bovine respiratory disease, oxytetracycline, tulathromycin

ABSTRACT

A series of trials were conducted in feedlots in Italy to investigate the efficacy of gamithromycin in the prevention and treatment of bovine respiratory disease (BRD) in newly arrived cattle. Three studies were conducted on its preventive efficacy when compared to an untreated control, a long-acting oxytetracycline formulation or tulathromycin. The therapeutic responses to tulathromycin and gamithromycin were compared in the therapeutic study. Preventive treatment with gamithromycin significantly reduced the morbidity due to BRD by 86%, 86% and 35% compared to the untreated control group, the oxytetracycline group and the tulathromycin group respectively. In the therapeutic trial, the number of animals that required re-treatment during the 14 days following the initial medication was significantly reduced in the gamithromycin group, compared to the positive control group. These results suggest that the dual therapeutic and preventive action of gamithromycin provides a valuable addition to the veterinarians' armamentarium for the medical management of BRD.

INTRODUCTION

Bovine Respiratory Disease (BRD) is a common, complex condition of young cattle. It is common primarily because, compared to other domestic animals, cattle have a relatively small lung volume and less efficient pulmonary function, and are therefore vulnerable to perturbations of the respiratory tract rendering them more susceptible to infections. [1,2] Secondly, the many pathogens that are associated with disease are common themselves and frequently occur as commensals in healthy animals. [3,4] Thirdly, because many of the risk factors that are associated with BRD, such as mixing [5,6] and transportation [7,8] of animals, are integral to commercial cattle production. [9]

The complexity of BRD is a consequence of the variety of risk factors that can be involved, [10,11] the diversity of viral and bacterial agents that can be present, [12,13] the nature of the inflammatory response in the lungs,[14] and associated pathology. [15-17] In addition, innate and immune responses

vary amongst individual cattle, in part due to genetic differences. [18,19]

BRD remains the most important single cause of mortality and morbidity within the cattle feedlot industry, regardless of geographical location,[20-23] and correspondingly, is responsible for losses and costs that undermine the profitability of such enterprises.[19,24] Various measures to mitigate the risk and impact of BRD, including vaccination against viral and/or bacterial pathogens,[25,26], pre-conditioning of cattle before transport to the feedlot,[6,27] and sympathetic management on arrival,[28] have been studied and implemented, but none are completely effective in preventing BRD.

Because of the central importance of bacteria - Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma spp in BRD, and because there are currently no antiviral drugs registered for cattle, antibiotics are the cornerstone for the treatment and control of BRD. Approaches to the use of antibiotics in BRD are normally classified as either therapeutic or preventive, which can be defined as:

- Therapeutic:Treatment of individual cattle that are suffering from clinical BRD.
- Preventive: Simultaneous treatment of cohorts of cattle in order to help prevent them from acquiring dangerous loads of pathogenic bacteria. Preventive can be further sub-divided into
  - o Prophylactic: Treatment of whole groups of apparently healthy cattle, determined to be at high risk of BRD
  - o Metaphylactic: When the number of cases of BRD within a group reaches a threshold, the remainder of the in-contact animals are treated simultaneously in order to restrict the spread and impact of BRD.[29]

Irrespective of these approaches, the objectives common to all are to reduce bacterial populations in the lungs in order that clinical and pathological changes can be reversed or prevented, and to reduce the overall bacterial pathogen load within the group, with the aim of reducing transmission within and between cohorts.

Gamithromycin is a novel 7a-azalide that has recently been developed for the treatment and prevention of bovine respiratory disease. The compound belongs to the 15-membered semi-synthetic macrolide antibiotics of the azalide sub-class with uniquely positioned alkylated nitrogen at 7a-postion of the lactone ring. As a class, the azalides are characterised by having low serum concentrations, high tissue concentrations,and extended tissue elimination half-life.[30] They also preferentially accumulate in host defence cells, predominantly polymorphonuclear leukocytes, and macrophages, which can enhance the exposure of some bacterial pathogens to the antibiotic.[31]

Gamithromycin has been developed as single subcutaneous administration in cattle to provide clinical efficacy against respiratory diseases while minimizing stress from animal handling and maximizing compliance with treatment regimens. Following subcutaneous injection at 6 mg/kg, absorption is rapid and average plasma concentrations reach a maximum within twenty-four hours of administration.[32] Gamithromycin is extensively and rapidly distributed in lung tissue where, concentrations reach 18.5 μg/g 24 hours after injection. Concentrations of gamithromycin in lung are 247 to 410 times higher than in plasma over the period from 1 to 15 days post-injection. The high volume of distribution (Vss) of 24.9 L/kg after intravenous administration is reflective of this finding and the low level of binding to plasma proteins (26%) indicates that the availability of gamithromycin in tissues should be high.32

In studies involving field isolates from cattle in various European countries, gamithromycin was shown to have minimum inhibitory concentration (MIC90) values of 0.5, 1, and 1 μg/mL against M. haemolytica, P. multocida, and H. somni, respectively, and corresponding minimum bactericidal concentrations (MBC90) values of 1, 2, and 2 μg/mL.[32,33] Field studies

have shown that the pharmacokinetics and pharmacodynamics are reflective of clinical responses in that a single subcutaneous dose of gamithromycin at 6 mg/kg body weight provides rapid therapeutic efficacy in BRD and persistent activity to control existing and to prevent new infections for an extended period.[33]

The studies reported here were conducted under commercial feedlot conditions in Italy within a development program to extend the European field data that have already been generated for the registration of gamithromycin (Zactran®).

MATERIALS AND METHODS

An outline of the four studies that contribute to this paper is provided in Table 1. All the procedures were conducted according to the guidelines of the Council Directive 86/609/EEC of 24 November 1986 on the protection of animals used for experimental and other scientific purposes (European Communities, 1986) and to "The welfare for cattle kept for beef production" of the Scientific Committee on Animal Health and Animal Welfare, 2001.

ALLOCATION

For the three prevention studies, the normal procedures were as follows:

- The animals arrived from France at the Italian feedlots in trucks containing approximately 60 cattle each.
- The cattle from each consignment were off-loaded and randomly divided into two batches to ensure that the subsequent treatment groups were evenly matched for origin.
- Pens, which typically had space for around 60 animals, were then filled sequentially with batches of cattle from the trucks to ensure an even distribution within each pen.

After arrival and allocation to pens, the cattle were then processed through a handling race on Friday and Saturday according to the normal procedures for each feedlot, which included weighing as well as medication. The induction treatments comprised a range of commonly used vaccines and parasiticides (Table 1). After processing, animals were treated alternatively in order of presentation with either gamithromycin or the control antibiotic except for trial 1 in which the control group was unmedicated, but was not treated with a placebo. In the therapeutic study (trial 4), the clinically affected animals were separated from the main group of cattle and then treated as above.

TREATMENT GROUPS

The three prevention studies were in effect a progression from the first, in which the control group received no antibiotic treatment, to the second, in which a positive control group was treated with a conventional long-lasting oxytetracycline product at 300 mg/kg, to the third, in which a relatively new product with prolonged activity was used – tulathromycin at a dose of 2.5 mg/kg. The therapeutic study was opportunistic insofar as a group of young Limousin heifers within a larger batch of animals had severe clinical signs of BRD at or very soon after arrival. They were separated from the main group, divided into two batches, and treated according to allocation with either gamithromycin or tulathromycin, in both cases, plus ketoprofen at 3 mg/kg.

In Trial 1, in an effort to limit contact between treated and untreated animals, the treatment groups were kept in separate pens. In trials 2 and 4, the animals in each treatment group were mixed within pens. In trial 3, the cattle were penned separately by treatment groups.

In trial 1, naso-pharyngeal swabs were taken from a random selection of 16 animals prior to treatment at the start of the study and from 29 control animals, clearly affected by BRD, on day 7 and 14.

MANAGEMENT

In each study, trial cattle were subject to the same management in terms of feeding, watering, handling, and housing as was normally carried out at each site. In trial 1 the cattle were penned in outside yards with shelter, in the other studies, the cattle were

Table 1. *Background details of the four studies.*

Trial#, type & Farm	Animals				Induction treatment*	Treatment groups	Duration (clinical)	Evaluations
Prevention	Number	Sex	Breed	Starting weight				
1. Verona	250	Male	Charolais	~350 kg	**Vaccination** IBR, PI3, Pasteurella **Parasiticide** Ivermectin + clorsulon	125 animals gamithromycin 125 animals untreated control	14 days	Microbiology Morbidity Problem cases Growth
2. Alessandria	470	Male & female	Charolais Limousin Ch x Lim	~345 kg	**Vaccination** IBR, PI3, RSV, BVD **Parasiticide** Ivermectin + clorsulon	235 animals gamithromycin 235 animals oxytetracycline	14 days	Morbidity Problem cases
3. Alessandria	1136	Male & female	Charolais Limousin Ch x Lim	~325 kg	**Vaccination** IBR, PI3, RSV, BVD **Parasiticide** Ivermectin + clorsulon	568 animals gamithromycin 568 animals tulathromycin	14 days	Mortality Morbidity Problem cases Growth
Therapy								
4. Alessandria	24	Females	Limousin	~258 kg	**Vaccination** IBR, PI3, RSV, BVD **Parasiticide** Ivermectin + clorsulon	13 animals gamithromycin + ketoprofen 11 animals tulathromycin + ketoprofen	14 days	Animals requiring 2nd treatment Problem cases

**IBR=Infectious Bovine Rhinotracheitis; PI3=Parainfluenza 3 virus; RSV=Respiratory Syncitial Virus; BVD=Bovine Virus Diarrhoea virus.*

kept in open-sided sheds.

OBSERVATIONS

Following allocation and treatment, the trial animals were examined daily by the on-site veterinarian, who was blinded as to the identity of the treatment groups. Any animals that were seen to be affected by BRD during the 14-day observation period were examined clinically and treated individually, at the discretion of the veterinarian, with antibiotics and non-steroidal anti-inflammatory agents (NSAIDs). The number of BRD-affected animals was used to calculate morbidity rates and in addition, re-treatments were recorded. If individuals were removed from the main pens to hospital pens, they were recorded as 'problem animals.' Live weight was measured at the start of the studies for the purposes of ensuring accurate dosing of any treatments, and again on Day 30 in Trials 1 and 3 to calculate short-term growth rates.

STATISTICAL ANALYSIS

In trial 1 body weight and average daily gain (ADG) were individually recorded and statistically analyzed using a General Linear Model procedure (SAS institute 2004). The following model was fitted: $Yim = \mu + Ti + TPik + eikm$ where Yikm is the dependent variable, μ is the overall mean, Ti is the fixed effect of the treatment, TPik is the fixed effect of treatment x pen interaction, and eiklm is the random residual error. Due to lack of significance ($P>0.05$) of treatment x pen interaction, this effect was not considered.

In trial 3 body weight and average daily gain (ADG) were individually registered and statistically analyzed using a General Linear Model procedures (SAS institute 2004). The following model was fitted: $Yiklm = \mu + Ti + TPik + bPijlk + eiklm$ where Yikl is the dependent variable, μ is the overall mean, Ti is the fixed effect of the treatment, TPik is the fixed effect of treatment x pen interaction, b is the linear regression coefficient of the starting weight of the animals (Pijlk) on the dependent variable (Yiklm) and eiklm is the random residual error.

In all the trials the association among incidence of problematic animals, relapsing animals, and mortality was evaluated by means the $\chi 2$ test for a 2x2 contingency table using the FREQ procedure of SAS (SAS institute 2004).

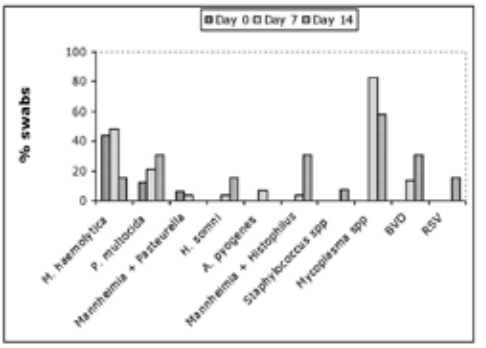
RESULTS

The main clinical results and their statistical significance are summarized in Table 2.

***Table 2**. Summary of clinical results in trials 1-4*

Trial number	Parameter	Treatment group		Significance (P)
1. Verona		Negative Control	Gamithromycin	
	% Morbidity	34.4	4.8	<0.0001
	% Problem animals	1.6	0.8	NS
2. Alessandria		Oxytetracycline	Gamithromycin	
	% Morbidity	14.5	1.7	<0.0001
	% Problem animals	5.1	1.7	<0.05
3. Alessandria		Tulathromycin	Gamithromycin	
	% Morbidity	14.6	9.3	0.006
	% Problem animals	1.8	0.9	NS
	% Mortality	0.7	0.4	NS
4. Alessandria		Tulathromycin	Gamithromycin	
	% Animals re-treated	81.8	30.8	0.004
	% Problem animals	27.7	0	0.04

Figure 1. *Trial 1. Pathogens isolated from naso-pharyngeal swabs Days 0 (pre-treament), 7 & 14 (untreated controls with clinical BRD)*



M. haemolytica = Mannheimia haemolytica
P. multocida = Pasteurella multocida
H. somni = Histophilus somni
A. pyogenes = Arcanobacterium pyogenes
BVD = Bovine Virus Diarrhoea
RSV = Respiratory Syncitial Virus

Trial 1

Microbiology

The identity and proportion of organisms isolated from the nasopharyngeal swabs are shown in Figure 1. Swabs that were taken prior to medication yielded bacterial pathogens only – M. haemolytica and P. multocida. However subsequent samplings of control animals with BRD 7 and 14 days later revealed an evolving and more diverse biota with the addition of several other pathogens, including H. somni, Arcanobacterium pyogenes, Staphylococcus spp, Mycoplasma spp. Respiratory Syncitial Virus (RSV) and Bovine Virus Diarrhoea (BVD) virus.

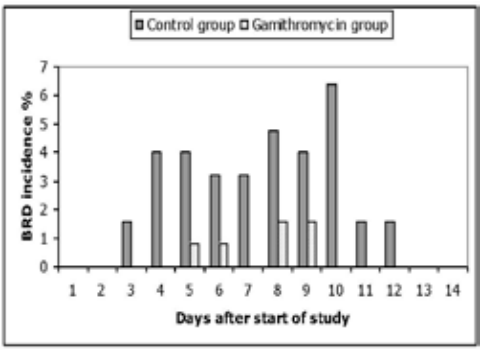
Clinical observations

Morbidity in the untreated control group (34%) was significantly (P<0.0001) different from that in the gamithromycin group (5%), but the percentage of problem animals in both groups was low (1.6% and 0.8% for the control and treated groups respectively) and not significantly different. The incidence pattern for BRD over the 14-day observation period is shown in Figure 2.

Growth

There was a significant (P=0.0001) difference between the daily growth rate of the control group, 1.08 kg, and the treated group, 1.83 kg, over the first 30 days of the study.

Figure 2. *Trial 1. Pattern of BRD morbidity Days 0-14*



Trial 2

Clinical observations

Morbidity in the oxytetracycline group of animals (15%) was significantly (P<0.0001) different from that in the gamithromycin group (2%), and there was also a significant (P<0.05) difference in the percentage of problem animals (4.8% and 1.6% for the oxytetracycline and gamithromycin groups respectively). The incidence pattern for BRD over the 14-day observation period is shown in Figure 3.

Trial 3

Clinical observations

Morbidity in the tulathromycin group (14%) was significantly (P<0.05) different from that in the gamithromycin group (9%). The percentage of problem animals and mortality in both groups was low (1.6% and 0.9%; 0.6% and 0.4% for the tulathromycin and gamithromycin groups respectively) and not significantly different. The incidence pattern for BRD over the 14-day observation period is shown in Figure 4.

Growth

There was no significant difference between the daily growth rate over the first 30 days of the study of the two groups (1.03 kg and 1.10 kg for the tulathromycin and gamithromycin groups respectively.

Figure 3. *Trial 2. Pattern of BRD morbidity Days 0-14*

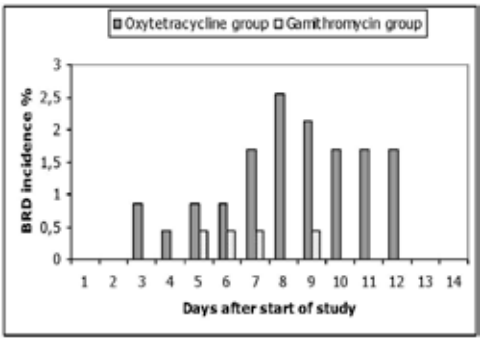


Figure 3. *Trial 3. Pattern of BRD morbidity Days 0-14*

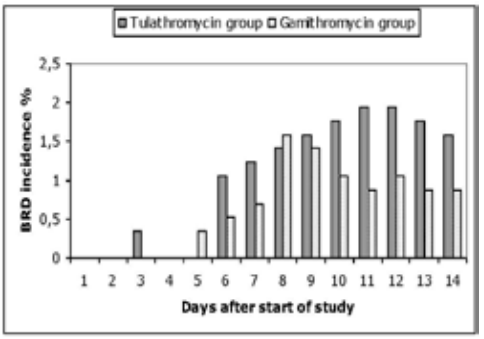
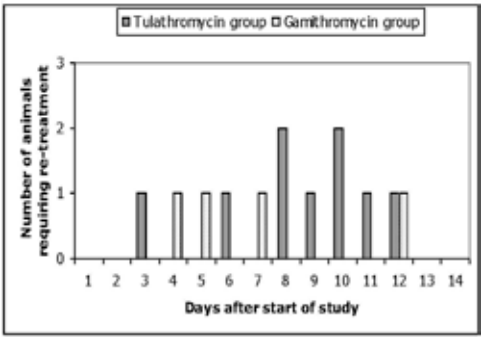


Figure 5. *Trial 4. Pattern of re-treatments for BRD, Days 0-14*



Trial 4

Clinical observations

Following the initial therapeutic treatment on Day 0, the proportion of heifers that required a 2nd treatment over the subsequent 14 days differed significantly (P=0.004) between the tulathromycin group (82%) and the gamithromycin group (31%). The percentage of problem animals also differed significantly (P=0.04) between the groups (28% and 0% for the tulathromycin and gamithromycin groups respectively). The incidence pattern of the animals requiring a 2nd treatment for BRD over the 14-day observation period is shown in Figure 5.

DISCUSSION

The complexity of BRD, particularly in terms of the range of pathogens that may be present and the severity of lung pathology, means that the outcomes of antibiotic treatment can be correspondingly variable. Examples from the scientific literature indicates a range of responses from <50% to >90% success in both therapeutic and prevention studies, [34-36] irrespective of the antibiotic that was used, although within studies, there may be differences in efficacy between products. The performance of gamithromycin in the current studies falls within this range, but direct comparisons are not possible because of differences in protocol etc. For logistical reasons, it was not possible to continue the intensive clinical observations for more than 14 days after treatment in this series of studies and this could be seen as a shortcoming when compared to studies that were conducted for longer. Nevertheless in trials 1 and 2, the morbidity had declined to zero by the end of the 14 days. in contrast, in Trial 3, the outbreak of BRD continued up to Day 14. Nevertheless, the efficacy rates reported over a longer period, eg, 60 days are generally reflective of results at 14 days, so the

success rate over a 14-day period can be taken as indicative of longer term results. [37]

The microbiological evaluations in trial 1 showed that on arrival the majority of sampled cattle harboured M. haemolytica and/or P. multocida the predominant organisms involved in the classical 'transit' or 'shipping' fever of cattle.38 Subsequently other bacteria were isolated and, most notably Mycoplasma spp became the most common pathogen. The other observation of note is the isolation of BVD virus on days 7 and 14, which strongly indicates the presence of individual cattle amongst the arrivals that were persistently infected with the virus. As BVD is known to result in general and local immunosuppression in BRD 39, its presence is likely to exacerbate the impact of the disease. The continued preventive efficacy of gamithromycin throughout this 14 day period during which the mix of pathogens changed supports its versatility as a BRD treatment.

CONCLUSION

It is important that antibiotics are used in a rational and controlled way in order to optimise their therapeutic effectiveness and to avoid unnecessary use and over-dependence.[40,41] Because feedlot cattle are frequently considered to be at high risk of BRD, mass preventive treatments before transport or on arrival are commonly used and are effective [36,42]. In addition, some studies have shown that selective treatments on arrival, based on body temperature, can provide equivalent levels of control to mass treatments.[34,43] The introduction of gamithromycin, with its pharmacokinetic and clinical profile of rapid therapeutic activity and prolonged preventive efficacy, offers additional opportunities for managing BRD on commercial farms.

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*This project was funded by Merial SAS, 29 avenue Tony Garnier, Lyon 69007, France - 1 -

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