Evaluation of the Efficacy of Zactran® Injectable Solution (150 mg gamithromycin/ml) in the Control of Bovine Respiratory disease in Germany in Comparison to Draxxin® Injectable Solution (100 mg Tulathromycin/ml)

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ABSTRACT

A field trial was conducted to evaluate the efficacy of Zactran injectable solution (150 mg gamithromycin/ml) in the control of bovine respiratory disease in comparison to Draxxin injectable solution (100 mg tulathromycin/ml) on a German commercial calf rearing/fattening farm.

One hundred and twenty newly arrived Brown Swiss male calves judged to be at high risk of developing bovine respiratory disease were split into two equal groups. The animals in each group were treated either with gamithromycin at 6 mg/kg or with tulathromycin at 2.5 mg/kg by subcutaneous injection. All animals were weighed individually on Days 1, 69, and 100. Weight gain was defined as the main criterion for comparison in this study. Animals treated with Zactran had numerically higher weight gains throughout the study, although differences between those treated with Zactran and Draxxin were not statistically significant.

INTRODUCTION

Bovine respiratory disease (BRD) is one of the most important and costly diseases in both dairy and beef-fattening farms (Biss, 1994; Griffin, 2010). The disease leads to short- and long-term loss of performance and can be fatal. Poor ventilation, abrupt weather changes, weaning, commingling, and transport all contribute to physiological stress, which makes cattle more susceptible to air-borne infectious agents. Cattle may become infected first by viral agents such as bovine viral diarrhoea (BVD), bovine respiratory syncytial virus (BRSV), infectious bovine rhinotracheitis, and parainfluenza virus 3 (Pi3). These viruses can damage the bovine respiratory tract, allowing bacterial pathogens, like *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, to colonise and proliferate in the lungs (Cusack, 2003; Duff, 2007; Step, 2008).

In addition to farm management techniques, the standard methods for control and treatment of BRD are based on vaccination and antibiotic treatment (Step, 2008). As animal welfare and the use of antibiotics in meat production are important issues for the public as well as farmers and veterinarians, animals need to be managed and medicated responsibly in order to ensure that health remains a top priority. This principle means that sick animals must be treated quickly, and their pen mates also must be protected against the spread of bacterial infection if deemed necessary by the use of antibiotics. Prompt and/or pre-emptive treatment can speed recovery and reduce the risk of chronic BRD cases.

The azalide gamithromycin is a 15-membered semi-synthetic macrolide antibiotic that is approved in Europe and elsewhere for both the treatment and prevention of BRD. After a single subcutaneous dose at 6 mg/kg, gamithromycin shows fast therapeutic and persistent preventive activity (Forbes, 2010; Huang, 2010). Another macrolide antibiotic, tulathromycin, belonging to the 15-membered trianilide sub-group, is also approved for prevention and treatment of BRD (Nowakowski, 2004).

To date, only one study has been published in which the performance of BRD-affected animals treated with either gamithromycin or tulathromycin has been compared under European feedlot conditions (Sgoifo Rossi, 2010). The objective of the present study was to compare the performance of both gamithromycin and tulathromycin in the prevention of BRD in young dairy calves.

MATERIALS AND METHODS

Animals

The trial was conducted on a commercial farm under field conditions. The farmer purchased the animals from multiple origins via a trader, mainly from calf-markets in southern Germany. The calves were commingled and shipped overnight in a trailer.

Allocation

A total of 120 male Braunvieh (Brown Swiss) calves around 33-35 days of age and weighing on average 67 kg arrived on Day 0 and were split randomly into two equivalent groups of 60 animals each.

Husbandry

The two groups were housed in separate pens within the same airspace and the same housing conditions. The pens had two equally sized, freely accessible areas. One was covered with fresh straw, and the other was made of slatted concrete floor. Milk was delivered individually to each animal using a transponder-operated device; water was available ad libitum at all times.

Veterinary Care

On arrival, all animals were vaccinated with a commercial respiratory live-vaccine for Bovine Respiratory Syncytial Virus (BRSV) and Parainfluenza 3 Virus (Pi3), and were treated 2 weeks after arrival with an ivermectin-based product against parasites. In addition, in accordance with standard veterinary practice for such calves, trimethoprim/sulphadiazine was administered orally from Day 1 to Day 10, and neomycin sulphate orally for 6 days, starting on Day 1, in order to mitigate bacterial enteritis.

Animals were supervised by the farmer, and any sick animals were treated according to standard protocols (which were recorded). Animals in both groups were managed in the same manner, including the allocation to subsequent medical treatments in response to respiratory problems. Animals that died were examined in the Chemisches und Veterinäruntersuchungsamt Münster. Animals were handled according to standard production practices and with due regard for their welfare.

Clinical Observations and Sampling

All animals were weighed, and their temperatures and respiratory scores measured and recorded the day after arrival (Day 1). The respiratory scores were based on a range from 0 for an animal with no observable abnormalities in respiratory function, in steps of one to a score of 3 when an animal was in severe respiratory distress (Lechtenberg, 2010a).

Respiratory scores

- 0 = normal: no abnormal respiratory symptoms were present. Respiratory rate and effort were appropriate for the environment.
- 1 = Mild respiratory distress: serous nasal or ocular discharge and/or cough.
- 2 = Moderate respiratory distress: mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
- 3 = severe respiratory distress: marked increase in respiratory rate or effort including one or more of the following: open mouth breathing, abdominal breathing, or extended head.

Pre-treatment nasal swabs were taken from 10 randomly selected animals in each group on Day 1. Swabs were placed in media and delivered to the LUFA Nord-West Laboratory in Oldenburg. The swabs were cultured for bacterial pathogens, including Pasteurellae. Five swabs from each group were pooled, and a PCR was run to detect *Mycoplasma bovis*, BVDV, BRSV and Pi3, if present.

On Days 8 and 14, temperatures were recorded from 15 randomly selected animals, and nasal swabs from 5 randomly selected animals were taken in each group. The swabs were cultured for bacterial pathogens (Pasteurellae). The 5 swabs from each group were pooled, and a PCR was run to detect *Mycoplasma bovis*, BVDV, BRSV and Pi3, if present.

On Day 28, nasal swabs from five randomly selected animals were taken in each group, and the swabs were cultured for bacterial pathogens (Pasteurellae). The 5 swabs from each group were pooled, and a PCR was run to detect *Mycoplasma bovis*, BVDV, BRSV and Pi3.

All animals were weaned on Day 47. On Day 69, all animals were weighed, and temperature and respiratory scores were recorded from 30 randomly selected animals in each group. On Day 100, all animals were weighed at study conclusion.

Treatment

Group D1

On Day 1, one group of 60 calves was treated with an injectable solution containing 100 mg tulathromycin/ml (Draxxin), administered once by subcutaneous injection at the rate of 1 ml/40 kg live weight (2,5 mg tulathromycin/kg) with a maximum of 7,5.

Group Z1

On Day 1, the second group of 60 calves was treated with an injectable solution containing 150 mg gamithromycin/ml (Zactran) administered once by subcutaneous injection at the rate of 1 ml/25 kg live weight (6 mg gamithromycin/kg) with a maximum of 10 ml at one site.

Statistical Analysis

Linear regression models were utilized to evaluate the effect of the treatment groups on the dependent variables “absolute weight gain between Day 1 and Day 69” and “absolute weight gain between Day 1 and Day 100”. Z1 was chosen as the reference category for the treatment. To take the different baseline values into account, the following covariates were included in the models:

Table 1. *Descriptive statistics of baseline values for both groups*

	Z1		D1	
	Mean (Standard deviation)	Min - Max	Mean (Standard deviation)	Min - Max
Weight (Day 1) in kg	66.2 (5.1)	54.0 – 75.5	69.6 (6.6)	52 – 80.5
Temperature (Day 1) in degree Celsius	39.2 (0.5)	38.4 – 40.8	39.0 (0.5)	38.0 – 40.1
	Count	Percent	Count	Percent
Respiratory score (Day1) = 0	19	31.7%	25	42.4%
Respiratory score (Day1) = 1 or 2	41	68.3%	34	57.6%

- Difference to the mean weight on Day 1 in kg (individual initial weight minus mean initial weight)
- Difference to the mean rectal temperature on Day 1 in Degrees Celsius (individual initial temperature minus mean initial temperature)
- Respiratory Score on Day 1 (as a categorical variable with respiratory Score=0 as reference category and respiratory Score=1 or 2 as combined alternative category)

Subtraction of averages was done to assess regression coefficients that are directly interpretable. A constant term was included as well, which can be translated as average weight gain of an animal with all covariates to be equal zero respectively, the reference category. This means an animal from the Z1 group with an average weight and temperature and a respiratory score of 0.

All analyses were conducted with the statistical software package R (version 2.13.0).

RESULTS

Clinical Observations

Adverse reactions were not observed in any animal treated with gamithromycin or tulathromycin.

During the trial, one animal from the tulathromycin group had to be humanely euthanized on welfare grounds on study Day 27 due to severe, unresponsive BRD. A necropsy at the Chemisches und Veterinäruntersuchungsamt in Münster showed that the animal had a severe bacterial pneumonia. Because the weight gain could not be determined, this calf was excluded from the analysis.

Re-treatment

All animals in both groups (D1 and Z1) were medicated orally with doxycycline from Day 15 to 20 on veterinary advice because of low grade BRD. In addition, during the first 30 study days, five animals from the tulathromycin group (D1) and five animals from the gamithromycin group (Z1) had to be retreated because they showed signs of BRD. From Day 30 to Day 100, five animals from the tulathromycin group (D1) and 1 animal from the gamithromycin group (Z1) had to be retreated due to respiratory problems.

Microbiology

From the pre-treatment nasal swabs taken on Day 1, *M. haemolytica* and *M. bovis* were isolated from animals destined to be in the gamithromycin group (Z1), whilst only M. haemolytica was found in the group subsequently treated with tulathromycin (D1). No viruses - BVDV, BRSV and Pi3V - were detected in any of the pre-treatment pooled samples.

From Day 14 onwards, *M. bovis* was

Table 2. *Linear regression model to assess the influence of the treatment and the additional covariates on the weight gain between Day 1 and Day 69*

	Regression coefficient	*p*-value
Constant	74.766	<0.001
Difference to the mean weight on Day 1 in kg	0.375	0.033
Difference to the mean rectal temperature on Day 1 in Degrees Celsius	0.111	0.957
Respiratory Score (Day 1)= 1 or 2	3.815	0.072
treatment group = D1	-2.572	0.237

According to the statistical model, an average animal from the gamithromycin group gained 74.8 kg between Day 1 and Day 69, whereas an animal from the tulathromycin group gained 2.6 kg less over the same time period (p=0.237). Additionally, the initial weight had a significant influence on the weight gain (p=0.033). With each kg above the mean initial weight, the calf is expected to gain 0.375 kg more than the average.

detected in pooled samples from both the gamithromycin and the tulathromycin groups; BRS-virus was also detected in the gamithromycin pool on Day 14.

Weight Gain

One hundred nineteen animals were taken into account for all statistical analyses. The mean initial weight in this sample was 67.9 kg. The mean rectal temperature on Day 1 was 39.1.

According to the statistical model, an average animal from the gamithromycin group gained 74.8 kg between Day 1 and Day 69, whereas an animal from the tulathromycin group gained 2.6 kg less over the same time period (p=0.237). Additionally, the initial weight had a significant influence on the weight gain (p=0.033). With each kg above the mean initial weight, the calf is expected to gain 0.375 kg more than the average.

By Day 100, an average animal from the gamithromycin group would have gained 114.2 kg, whereas an animal from the tulathromycin group would have gained 1.8 kg less over the same time period (p=0.515). The influence of initial weight was not significant anymore, although animals with a higher initial weight had a slight advantage again.

DISCUSSION

In addition to regulatory actions aimed at reducing the use of antibiotics in animal production, farmers and veterinarians are also interested in reducing the use of antibiotics, providing that animal health and production does not suffer. To keep animals in good health, much can be done in terms of housing improvements and vaccination. One of

Table 3. *Linear regression model to assess the influence of the treatment and the additional covariates on the weight gain between Day 1 and Day 100*

	Regression coefficient	*p*-value
Constant	114.196	<0.001
Difference to the mean weight on Day 1 in kg	0.418	0.068
Difference to the mean rectal temperature on Day 1 in Degrees Celsius	-0.254	0.924
Respiratory Score (Day 1). = 1 or 2	6.581	0.018
treatment group = D1	-1.847	0.515

the limitations of vaccination is that, with the possible exception of vaccines administered via the intra-nasal route, the onset of protective immunity is too late to cover the time when recently transported animals are most at risk of BRD. BRD frequently occurs within 2-3 weeks of arrival on a new farm (Andrews, 1976; Babcock, 2010; Snowder, 2006). Because the risks of an outbreak of diseases like BRD cannot be completely eliminated, particularly when young calves from different origins are commingled and shipped to a fattening farm, the correct use of antibiotics in cattle rearing farms plays an important role in reducing the incidence and impact of BRD (Guigère, 2011; Lechtenberg, 2011a; Pardon, 2011). In a herd with good control of BRD, fewer antibiotic treatments are needed for re-treatment of chronic cases. For both the treatment and the prevention of BRD, fast acting and long-lasting antimicrobial agents are widely used. Single-shot, long-lasting antibiotic treatments offer a convenient tool to manage BRD responsibly.

This study was conducted under field conditions on a commercial farm taking into consideration the owner's requirements and local veterinary advice. For welfare and economic reasons, all sick animals were treated immediately by the local veterinarian in charge. As all the calves were considered to be at high risk of developing BRD and bacterial enteritis, additional antibiotic treatment was given to the whole group, based on the veterinarian's judgment and previous experience on this farm.

In a parallel trial at the same time under the same conditions (data not shown), a second group of 120 calves was treated twice – on Days 1 and 6 with gamithromycin and tulathromycin, to see if a longer period of antibiotic cover would be of additional benefit. The second treatment did not lead to better control of BRD or an improved daily weight gain in the calves compared to the group that received the injectable macrolide only once on Day 1.

Another interesting aspect of the study was that animals with a higher initial respiratory score gained more weight by Day 69 and 100 than animals with a normal initial respiratory score (Tables 2 & 3). The animals in this trial came from multiple origins in the southern part of Germany, where smaller dairy farms, run by part-time farmers are not uncommon. The health-status of calves born on these farms may vary according to the resources and expertise available. Such calves are likely to be at higher risk of various infectious diseases, including BRD, and they may have arrived on the trial farm already ill as reflected with the higher respiratory scores. It appears from the results of this study that many of these calves may have exhibited compensatory growth following adaptation to the high quality of husbandry and medication at the receiving farm under study conditions.

M. bovis is commonly isolated from cases of BRD, but its role in the initiation of disease and in the maintenance of chronic infections remains unclear (Arcangioli, 2007; Lechtenberg, 2011a; Lechtenberg, 2011b; White, 2010). White could not detect any *M. bovis* positive calves at the day of housing. Subsequently, 20.6 % of the calves treated against BRD were tested positive for *M. bovis* (White, 2010). In a French feedlot, *M. bovis* occurred frequently and early in calf respiratory disease outbreaks, strongly suggesting that it is an initiating factor for BRD. Nevertheless in the same study, *M. bovis* was found to the same extent in both, apparently sick and healthy calves, (Arcangioli, 2007). In the present study, *M. bovis* was detected in only one pooled PCR sample taken on Day 1, whereas all pooled PCR samples were positive from Day 14 in both groups, gamithromycin (Z1) and tulathromycin (D1), indicating that the organisms had circulated amongst the animals following arrival.

Results of this study indicate that gamithromycin administered upon arrival is a useful medication for the control of bovine respiratory disease. Overall, animals treated with gamithromycin needed fewer re-

treatment for BRD than animals treated with tulathromycin. The weight gain showed no significant difference between the gamithromycin and the tulathromycin treated group though there was a trend to higher weight gain in animals in the gamithromycin group.

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REFERENCES

1. Andrews AH. Factors affecring the incidence of pneumonia in growing bulls. *Vet Rec* 1976; 98:146-149.
2. Arcangioli MA, Duet A, Meyer G, Dernburg A, Bézille P, Poumarat F, Le Grand D. The role of *Mycoplasma bovis* in bovine respiratory disease outbreaks in veal calf feedlots. *Vet J* 2008; 177:89-93.
3. Babcock AH, Renter DG, White BJ, Dubnicka SR, Scott HM. Temporal distributions of respiratory disease events within cohorts of feedlot cattle and associations with cattle health and performance indices. *Prev Vet Med* 2010; 97: 198-219.
4. Biss ME, Alley MR, Madie P, Hathaway SC. Lesions in the carcasses and viscera of very young slaughter calves condemned at post-mortem meat inspection. *N Z Vet J* 1994; 42:121-127.
5. Cusack PM, McMeniman N, Lean IJ. The medicine and epidemiology of bovine respiratory disease in feedlots. *Aust Vet J* 2003; 81:480-487.
6. Duff GC, Galyean ML. Board-invited review: recent advances in management of highly stressed, newly received feedlot cattle. *J Anim Sci* 2007; 85:823-840.
7. Forbes AB, Ramage C Sales J, Baggott D, Donachie W. Determination of the duration of antibacterial efficacy following administration of gamithromycin using a bovine *Mannheimia haemolytica* challenge model. *Antimicrob Agents Chemother* 2011; 55:831-835.
8. Griffin D, Chengappa MM, Kuszak J, Mcvey DS. Bacterial pathogens of the bovine respiratory disease complex. *Vet Clin North am Food Anim Pract* 2010; 26:318-394.
9. Guigère S, Tessman RK. Rational Dosing of Antimicrobial Agents for Bovine Respiratory Disease: The Use of Plasma Versus Tissue Concentrations in Predicting Efficacy. *Intern J Appl Res Vet Med* 2011; 9:342-355.
10. Huang RA, Letendre LT, Banav N, Fischer J, Somerville B. Pharmacokinetics of gamithromycin in cattle with comparison of plasma and lung tissue concentrations and plasma antibacterial activity. *J Vet Pharmacol Ther* 2010; 33:227-237.
11. Lechtenberg K, Daniels CS, Royer GC, Bechtol DT, Chester ST, Blair J, Tessman RK. Field Efficacy Study of Gamithromycin for the Control of Bovine Respiratory Disease in Cattle at High Risk of Developing the Disease. *Intern J Appl Res Vet Med* 2011a; 9:184-192.
12. Lechtenberg K, Tessman RK, Chester ST. Efficacy of Gamithromycin Injectable Solution for the Treatment of *Mycoplasma bovis* Induced Pneumonia in Cattle. *Intern J Appl Res Vet Med* 2011b; 9:233-240.
13. Nowakowski MA, Inskeep P, Risk J, Skogerboe TL, Benaoui HA, Meinert TR, Sherington J, Sunderland SJ. Pharmacokinetics and lung tissue concentrations of tulathromycin, a new triamilide antibiotic, in cattle. *Vet Ther* 2004; 5:60-74.
14. Pardon B, De Bleecker K, Dewulf J, Callens J, Boyen F, Catry B, Deprez P. Prevalence of respiratory pathogens in diseased, non-vaccinated, routinely medicated veal calves. *Vet Rec* 2011; 169,278.
15. Sgoifo Rossi CA, Vandoni SL, Bonfanti M, Forbes AB. Effects of arrival medication with gamithromycin on bovine respiratory disease in feedlot cattle in Italy. *Intern J Appl Res Vet Med* 2010; 8:87-96.
16. Snowder GD, Van Vleck LD, Cundiff LV, Bennett GL. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. *J Anim Sci* 2006; 84:1999-2008.
17. Step DL, Krehbiel CR, DePra HA et al. Effects of commingling beef calves from different sources and weaning protocols during a forty-two-day receiving period on performance and bovine respiratory disease. *J Anim Sci* 2008; 86:3146-3158.
18. White BJ, Hanzlicek G, Sanderson MW, Anderson DE, Larson RL. Mollicutes species and *Mycoplasma bovis* prevalence and association with health outcomes in beef feeder calves at arrival and initial treatment for bovine respiratory disease. *Can Vet J* 2010; 51:1016-1018.