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Determination of the Duration of Antibacterial Efficacy following Administration of Gamithromycin Using a Bovine *Mannheimia haemolytica* Challenge Model[▽]

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The antibacterial efficacy of gamithromycin administered once 1, 5, or 10 days prior to a challenge infection with *Mannheimia haemolytica* serotype A1 was evaluated. Forty calves were randomly allocated on day −11, restricted by body weight, to one of three treatment groups given gamithromycin at 6 mg/kg of body weight 10, 5, or 1 days before challenge or to an untreated control group. *M. haemolytica* A1 challenge infections were induced on day 0 by depositing 7.4×10^7 CFU at the bifurcation of the main bronchus using a bronchoscope. Clinical observations were made daily from the day of allocation to day 10, when necropsy was scheduled; three calves died or were euthanized *in extremis* on welfare grounds prior to scheduled necropsy. At necropsy the lungs were removed, pneumonic lesions were scored, and samples of lung tissue were cultured for *M. haemolytica*. The three groups of animals treated with gamithromycin before challenge had significantly lower lung *M. haemolytica* counts and fewer clinical signs of respiratory disease than did the saline-treated group. For most of the clinical parameters, the pattern of responses differed significantly ($P < 0.05$) between the gamithromycin-treated groups and the control group. There were no statistically significant differences between groups in the mean lung lesion scores, partly as a result of high individual variability, particularly within the control group. The administration of gamithromycin 1, 5, and 10 days prior to *M. haemolytica* A1 challenge resulted in a reduction in bacterial isolation from the lungs and a reduction in the severity of clinical disease.

Bovine respiratory disease (BRD) is one of the most significant causes of mortality, ill health, and production losses in young cattle (12, 17, 18, 26). It remains common, despite recent advances in chemotherapy, vaccination, and animal management, because of the complexity of infectious agents that can invade the lower respiratory tract (2) and because of the ubiquity of the stressors that can precipitate disease in cattle production (5, 12, 13, 15, 29).

Antibiotics remain key elements in the treatment and control of BRD because of the central role of bacteria in the development and severity of lung pathology (1, 3). Bacterial pathogens that are frequently isolated from clinical cases include *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, and these species appear to be able to act as primary pathogens insofar as prior invasion by viruses and/or coinfection is not a prerequisite for disease (6, 8, 22, 24).

The use of antibiotics in BRD can be broadly categorized as either therapeutic or preventive. Therapeutic use describes administration to individual animals that are showing overt clinical signs of BRD, whereas preventive use, which is also commonly referred to as metaphylaxis, involves the treatment of groups of animals deemed to be at high risk of developing BRD or to be in the preclinical stages (20). In therapeutic use, antibiotic activity should cover the course of clinical disease in sick animals so that relapses do not occur and pneumonic lesions are given time to resolve: this can be achieved by either the repeated administration of short-acting products or a single administration of a product with persistent efficacy. When antibiotics are used preventively, the exact status of each animal in the group at the time of treatment is not known; some may be incubating the disease, and others may not yet be infected. Thus, there is value in providing antibiotic cover over an extended period so that animals that have not already encountered infection will be protected by a later challenge.

Gamithromycin is a recently developed antibiotic of the azalide family currently (2010) licensed in the European Union and Canada for use in the treatment and control of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. The approved dosage is 6 mg/kg body weight, and it is administered as a subcutaneous injection: it is rapidly absorbed from this site, and peak plasma levels are achieved within 1 h. There is an equally rapid distribution from the plasma into the tissues, most notably the lung, where concentrations are maximal (mean, 18.5 μg gamithromycin/g) within 24 h: the ratios of lung to plasma concentrations exceed 200 for up to 15 days posttreatment when the mean lung concentration is 0.7 μg/g (14). The MIC_{90} values for the three pathogens in Europe are between 0.5 and 1 μg gamithromycin/ml (9), and drug concentrations in whole lung exceed these

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values for 12 to 15 days after administration (14); hence, prolonged antimicrobial activity can be anticipated.

The objective of this controlled, blinded, randomized study was to determine the length of time postadministration during which gamithromycin activity persisted at concentrations sufficient to counter an artificial intrabronchial challenge with *M. haemolytica*. This design simulates circumstances where the product may be used preventively in the field for groups of at-risk animals of unknown infection status. The study was conducted according to the criteria established by guidelines for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01) and the International Cooperation on Harmonization (VICH) technical requirements for registration of veterinary medicinal products, guideline 9 (good clinical practice), and according to Moredun Scientific's standard operating procedures (SOPs). All animals were maintained at all times in accordance with European Union and United Kingdom animal welfare regulations.

MATERIALS AND METHODS

Animals. Forty weaned dairy and dairy-cross calves (39 males and 1 female) were enrolled in the study; they were approximately 9 weeks old with a weight range of 48 to 101 kg when challenged with *Mannheimia haemolytica* on study day 0. The animals were free of bovine viral diarrhea virus (BVDV) viremia, as determined by antigen detection (10) at approximately 5 weeks of age; were in good health with no signs of BRD; and had low serum antibody titers (<1/16) against *M. haemolytica* serotypes A1 and A6, as determined by a serotype-specific indirect hemagglutination (IHA) test (11) at approximately 5 weeks of age. In addition, all animals were treated with florfenicol (Nuflor; Schering-Plough) intramuscularly at the manufacturer's recommended dose, not less than 14 days prior to the start of the study, to reduce the risk of bacterial respiratory infection occurring before the experimental challenge with *M. haemolytica* A1 on day 0.

The calves were individually penned and bedded on straw from arrival in multipurpose semicontainment accommodation, sharing the same air space. On the day of allocation (day −11), animals in the control (unmedicated) group were repenned so that there was no direct contact between test medicated and unmedicated animals. All calves were offered free access to hay and clean water at all times and fed 1 ± 0.1 kg concentrated calf ration twice daily.

Study design. The 40 eligible calves were randomly allocated on day −11, restricted by body weight, to one of four treatment groups: groups treated with gamithromycin once at 10 days (group 1), 5 days (group 2), and 1 day (group 3) before challenge and a challenge control group (group 4) treated with saline 1 day before challenge. Thirty-seven calves were available for challenge as a result of the loss of three calves after allocation due to bloat or respiratory disease. Therefore, at challenge on day 0, groups 1 and 2 consisted of 10 calves each, and groups 3 and 4 consisted of 9 and 8 calves, respectively.

All calves in groups 1 to 3 were treated once with 150 mg/ml gamithromycin as a subcutaneous injectable solution (Zactran; Merial Ltd., Duluth, GA) at 6 mg/kg, equivalent to 1 ml/25 kg of body weight. The challenge control calves (group 4) received 0.9% sterile saline solution as a control substance on day −1 (prechallenge) at 1 ml/25 kg of body weight subcutaneously. Calculated dose volumes were rounded up to the nearest 0.2 ml.

Treatments were administered in the neck region in front of the shoulder (left side) using sterile hypodermic syringes. Animals were observed immediately posttreatment for signs of adverse reactions.

The 37 animals remaining on day 0 were each challenged with approximately 300 ml of an *M. haemolytica* A1 phosphate-buffered saline diluted broth (nutrient broth 2; Oxoid) culture containing 2.33×10^5 CFU of *M. haemolytica* A1/ml by endobronchial deposition at the bifurcation of the main bronchus through a fiber-optic bronchoscope. The challenge doses for each calf contained an estimated mean of 7.4×10^7 CFU *M. haemolytica* A1. The challenge strain was isolated from a pneumonic calf in 1993, and its MIC of gamithromycin was confirmed to be 1 μg/ml prior to the start of this study.

Health and clinical observations. General health observations were conducted by experienced personnel twice daily at the morning and afternoon feeding times for all animals from arrival until the end of the study. Any animals showing signs of abnormal health were examined by a veterinarian.

Clinical observations were made twice daily (at least 5 h apart) on day −5 to day 10, ending at the morning observation (10 days postchallenge) prior to scheduled necropsy. On day 0, animals were observed prior to challenge and at approximately 3 to 4 h postchallenge. Clinical observations included the following parameters: rectal temperature in degrees Celsius, respiratory rate as breaths per minute, nasal discharge as a score between 0 (none) and 4 (mucopurulent), nature of respiration as a score between 0 (normal) and 3 (dyspnea), demeanor as a score between 0 (normal) and 3 (moribund), and coughing as a score between 0 (none) and 2 (moist). Clinical parameter scores were summed for each animal at each observation time to give a total clinical severity score. Respiration rate, nature of respiration, demeanor, coughing, and (where possible) nasal discharge were observed from outside the pen (while animals were resting) prior to entering the pen to record rectal temperatures. Calves that were showing severe depression and/or signs of respiratory distress before the scheduled end of the study were humanely euthanized, and the lungs removed and assessed by the methods detailed below.

Necropsy procedures. Calves that survived to day 10 (10 days after *M. haemolytica* challenge) were humanely euthanized. Following euthanasia, each calf was necropsied immediately. Lungs were removed from each animal, taking care not to damage any of the lung lobes. Lung lesions were recorded by estimating the amount of consolidation or other lesions, both visually and by palpation in each of the lobes. The percent gross involvement of lesions for each lobe was summarized and then weighted using the following percentages (based on ratios of individual lobes to total lung mass): left apical, 5%; left cardiac, 6%; left diaphragmatic, 32%; right apical, 6%; right accessory, 5%; right cardiac, 7%; right diaphragmatic, 35%; and intermediate, 4%. The weighted lung lobe values were then summed to yield the consolidated lung lesion score (percent lung lesions) for each animal (16).

Tissue samples of approximately 1 g to 2 g each were excised from each lung at necropsy from eight standard sites in the lungs and pooled to give four samples per calf. Consolidated (pneumonic) sites in each of the designated areas were sampled preferentially. Each pooled lung sample was weighed, placed into a bag together with 9.0 ml of peptone water to provide a nominal dilution of 10^{-1}, and homogenized for 30 s. A 20-μl aliquot of homogenate was diluted in 180 μl of peptone water in a sterile U-well microtitration plate to give a 10^{-2} dilution. This dilution process was repeated until the homogenate had been diluted to 10^{-7}. Duplicate 10-μl aliquots of each homogenate dilution from 10^{-1} to 10^{-7} were placed onto the surface of a well-dried blood agar plate. After samples were dry, the plate was incubated overnight at 37°C (±2°C). Plates were inspected for typical colonies of *M. haemolytica* (smooth, circular, greyish colonies 1 to 2 mm in diameter and usually hemolytic). If present, colonies were counted, and at least one colony per calf upon each sampling occasion was identified to confirm the presence of *M. haemolytica* according to colony morphology and Gram stain results. The *M. haemolytica* CFU per gram of lung tissue was calculated.

Data handling and statistical analyses. Untransformed individual animal scores for each variable, including consolidated lung lesion scores, total clinical severity scores (nature of respiration, nasal discharge, demeanor, and cough scores), rectal temperatures, respiratory rates, and lung *Mannheimia haemolytica* colony counts, were used in the statistical analysis.

For lung lesion scores, a $\log_{10}$ transformation was applied to the data before analysis to ensure the homogeneity of variance, and the transformed data were analyzed by using a one-way analysis of variance.

Temperature and respiration rate data (from the day of challenge to 10 days postchallenge) were analyzed by using a linear mixed model with calf fitted as a random effect. This was equivalent to fitting a repeated-measures model with a uniform correlation structure. Parameters of the model were estimated by using the REML procedure in Genstat, and *P* values were estimated within Genstat by using modified F statistics. The relationship between the mean respiratory rate after challenge and lung lesion scores was investigated both graphically and by using simple linear regression on a log-log scale.

The individual clinical scores were measured on an ordinal scale. Differences between the groups were investigated in two ways. First, the maximum score attained by each animal after challenge for each individual trait was determined; the differences in the proportion of animals having particular scores, in the four groups, were tested by using a Fisher's exact test. Second, a mean total clinical score postchallenge was calculated for each calf. To avoid biases caused by the early euthanasia of some calves, the mean was calculated for the period from the afternoon of the day of challenge (day 0 p.m.) to the morning of day 2. A one-way analysis of variance was used to investigate any differences between the group means.

The number of *M. haemolytica* CFU in lung samples collected at necropsy from individual calves was determined by serial dilution. The data contained a large number of zero counts, and differences between groups, in the proportions

TABLE 1. Individual lung lesion scores, clinical scores, and recovery of *M. haemolytica*

Treatment group and calf (sex)	Lung lesion score	Highest individual clinical score	Cumulative mean daily clinical scores on days 1–9	Mean *M. haemolytica* CFU/g of lung
1 (treated on day −10)				
400692 (M)		1	1.5	0
501175 (M)	1.94	1	1.75	2.0×10^5
700681 (M)	2.09	2	5.0	2.0×10^3
101422 (M)	2.83	2	1.0	0
200506 (M)	6.99	2	3.5	0
100848 (M)	9.59	2	1.75	5.5×10^5
500876 (M)	9.81	3	4.25	0
200697 (M)	13.72	6	14.75	4.0×10^3
100709 (M)	27.81	3	3.75	8.4×10^4
100837 (M)	41.10	5	Euthanized day 4	6.3×10^6
2 (treated on day −5)				
400982 (M)	0.32	2	4.75	0
300832 (M)	0.56	2	2.75	0
601176 (M)	0.87	3	2.25	0
501732 (M)	2.01	4	3.0	0
600984 (M)	2.81	6	10.75	0
601550 (M)	4.18	2	2.25	0
101610 (M)	7.80	2	4.0	0
300708 (M)	12.73	3	5.75	2.8×10^3
300483 (M)	15.09	4	20.0	1.4×10^4
301144 (M)	17.70	4	22.75	7.2×10^3
3 (treated on day −1)				
700836 (M)	0.36	1	1.5	0
401731 (M)	2.04	0	0	0
500752 (M)	2.45	3	5.75	0
500845 (M)	5.07	1	1.25	0
201143 (F)	6.39	2	2.25	0
101735 (M)	8.03	3	1.75	0
201611 (M)	11.81	3	3.25	0
201553 (M)	11.93	3	6.0	1.5×10^3
300507 (M)	12.66	3	3.5	0
4 (control)				
401145 (M)	0.05	3	5.25	3.0×10^2
600870 (M)	0.8	3	4.5	3.7×10^2
700612 (M)	1.5	4	7.0	1.2×10^3
700538 (M)	1.9	3	7.25	4.8×10^2
401687 (M)	14.7	7	8.25	1.4×10^3
400875 (M)	22.4	6	20.5	5.0×10^5
701551 (M)	69.3	8	Died day 3	2.2×10^8
101142 (M)	74.4	7	Euthanized day 2	1.8×10^8

of calves having *M. haemolytica* colonies present, were investigated by using a Fisher's exact test.

RESULTS

None of the calves treated with gamithromycin showed any systemic or local adverse reactions or signs of toxicity.

The values for the main pathological, clinical, and bacteriological observations for individual calves are listed in Table 1. Between challenge and scheduled necropsy (day 10), three animals died or were euthanized *in extremis* with severe clinical signs of acute respiratory disease, two from group 4 and one from group 1. At necropsy, all three animals were confirmed as having pneumonic lesions with *M. haemolytica* counts on culture. All other animals survived to scheduled necropsy on day 10.

The distributions of rectal temperatures in all groups on the morning prior to challenge were very similar (with means of approximately 38.4°C). Postchallenge, there was a significant difference in the pattern of responses over time between the four groups ($P < 0.001$ for the group × time interaction effect). The mean temperature in all groups increased by 1.06°C to 1.83°C over the immediate 12-h period postchallenge but had dropped by the next morning after the challenge; however, the mean temperature in untreated controls (group 4) remained above the base level for most of the remainder of the study, whereas animals treated on day −1 (group 3) had close to a normal mean temperature from day 2 onwards.

The distributions of respiratory rates in all groups on the morning prior to challenge were very similar (means of approximately 35 breaths per minute). Postchallenge, there was strong evidence of a significant difference in the pattern of responses over time between the four groups ($P < 0.001$ for the group × time interaction effect). There was a sharp rise in the mean respiration rate on the day of challenge in all four groups to 72 to 93 breaths per minute; thereafter, the pattern of responses was inconsistent, although animals treated on day −1 (group 3) generally had the lowest mean respiratory rate.

The mean total clinical score postchallenge was calculated for each calf. To avoid a bias caused by the early euthanasia of some calves, the mean score was calculated for the period from the afternoon of the day of challenge (day 0 p.m.) to the morning of day 2. A one-way analysis of variance was carried out on the group mean scores. The means and patterns of clinical responses over this period were similar for treated groups 1, 2, and 3 (Table 2), and these were lower than the mean scores for group 4, the untreated controls ($P = 0.03$). This pattern was similar for the component measures of the total clinical score: respiration, coughing, nasal discharge, and demeanor.

The lung lesion score (percent lung lesions) of one animal from group 1 was not assessed or recorded at necropsy in error. A photograph (not shown) of this animal's lungs taken immediately after necropsy showed little evidence of lung pathology; hence, it can be assumed that the means for group 1 have not been underestimated as a consequence of this calf's data being absent from the analyses. The data for this animal were excluded from the statistical analysis of lung lesion scores but were included in all other analyses. A summary of the estimated lung lesion scores (percent lung lesions) for each group is given in Table 2.

The lung lesion scores were not consistent within each group of calves, with untreated controls (group 4) in particular showing considerable variability (Table 1). The scores for each group were skewed to the right, with the standard deviation approximately the same size as the mean for each group; consequently, there was no formal statistical evidence ($P = 0.76$) of any differences in mean responses between the four groups (Table 2).

The number of *M. haemolytica* CFU/g lung tissue was estimated for samples taken from four regions of each lung. Individual animals within a group had variable counts, and of the 37 animals in total, 19 animals had no bacteria recovered from any of the samples. There was no evidence of a difference in mean counts between the different areas of the lung, and a mean count, on a log scale using the transformation $\log_{10}(\text{count} + 1)$, was calculated for each animal. The numbers

TABLE 2. Mean clinical scores, lung lesion scores, and number of animals in each group positive for *M. haemolytica* postchallenge

Parameter	Value for group			
	1 (day −10)	2 (day −5)	3 (day −1)	4 (control)
No. of animals per group	10	10	9	8
Mean clinical score[a]	1.58	1.42	1.41	2.81
Mean lesion score (% lung lesions)[b]	12.88[d]	6.41	6.75	23.12
Range of lesion scores	1.94–41.10	0.32–17.70	1.55–12.66	0.05–74.37
No. of animals with positive lung tissue[c]	6	3	1	8

[a] $P = 0.03$.
[b] $P = 0.76$.
[c] $P = 0.0008$.
[d] Data not available for one animal.

of animals in each group from which *M. haemolytica* was recovered in at least one sample are shown in Table 2. Using a Fisher's exact test, there was a significant difference ($P = 0.0008$) in the proportion of animals with positive counts between the groups. *M. haemolytica* was recovered from all the untreated control animals (group 4), whereas only one of the nine animals treated on day −1 (group 3) had a positive count.

DISCUSSION

The experimental model used in this trial has produced reproducible results over many years in studies of bovine bacterial pneumonia, for example (25). The only difference in this experiment was that the observations continued for 10 days postchallenge rather than the normal duration of up to 4 days. There was a close relationship between the number of bacteria isolated from the lungs and the severity of the lung lesions in the three calves that died or were euthanized at 3 days of challenge. For the remainder of the animals, which were necropsied 10 days after the *M. haemolytica* challenge, the relationship was not quite so clear, but nevertheless, there was generally a positive relationship between the lung lesion score and the isolation of bacteria from the lungs and, indeed, the cumulative clinical scores. The extension of the recording to 10 days probably allowed the individual's innate defense mechanisms to help clear the lungs of pathogens from the challenge, thus weakening the relationship between lesions and bacterial populations because of differential rates of bacterial clearance and lesion development and resolution. These observations lend support to the validity of the model and also indicate that in the absence of any lesions suggestive of viral infections in the lung and in the absence in culture of any other bacterial species from the lung tissues, the observations can be attributed to the impact of *M. haemolytica* alone.

This study demonstrated that for most of the clinical, pathological, and bacteriological parameters studied, the effects of endobronchial challenge with *M. haemolytica* were mitigated in the groups treated with gamithromycin 1 to 10 days prior to infection. Statistically significant differences among the four experimental groups varied as a consequence of the high level of individual variability among the animals; this variability was particularly noticeable for the untreated control group (Table 1). As can be seen, five of the eight control animals had lung pathology comprising less than 2% of the total lung volume, cumulative mean daily clinical scores of <10.0 postchallenge, and/or *M. haemolytica* bacterial counts in the lungs of the order of 10^3 or less. The administration of the infective challenge of *M. haemolytica* was closely monitored, so it is highly unlikely that errors in dosing were made, and the presence of *M. haemolytica* in the lungs at the end of the study confirms the calves' infection status. Thus, it can be presumed that these individuals had a high level of innate resistance to infection with *M. haemolytica* and its associated pathology, which, given the standardized experimental conditions, was probably largely genetic in origin. There are several reports in the literature that have described genetic variation in cattle upon exposure to respiratory pathogens or vaccines (4, 19, 21, 27, 28).

The numbers of animals from which *M. haemolytica* bacteria were isolated from the lungs at necropsy were significantly different between the control group and the gamithromycin-treated groups. *M haemolytica* colonies were cultured from the lungs of all the control animals but from only a proportion of the gamithromycin-treated animals, providing evidence of an antibacterial effect of gamithromycin at all time points (days −10 to −1 prechallenge) that were evaluated. The mean whole-lung concentration of gamithromycin 10 days after administration was 1.19 μg/g in a study described previously by Huang et al. (14), which slightly exceeds the MIC for the isolate of *M. haemolytica* used in this experiment (1.0 μg/ml). Thus, assuming that this concentration of antibiotic is present at the site of bacterial colonization and multiplication in the lung and allowing for individual animal variability in pharmacokinetic behaviors, antibacterial activity would be expected in group 1 calves challenged 10 days after administration. The individual in group 1 that was euthanized approximately 56 h after challenge had a bacterial count of 6.29×10^6 in its lungs, which is 1 to 2 orders of magnitude lower than the counts of the two animals that died or were humanely euthanized in the control group. This calf had a total clinical score of 4 on the afternoon of the third day after challenge and was euthanized according to the criteria laid down by the protocol; at necropsy, 41.1% of its lung had pneumonic lesions.

Overall, we conclude that the administration of gamithromycin 1, 5, and 10 days prior to *M. haemolytica* challenge resulted in persistent antibacterial activity in the lungs, sufficient to reduce or eliminate bacteria, with a corresponding modulation of clinical signs and lung pathology in all groups, barring one calf treated 10 days before challenge. This model provides a robust test of an antibiotic using a challenge with a single respiratory pathogen, *M. haemolytica*, with an MIC higher than the MIC_{90} for current European field isolates (9), and this suggests that when administered preventively for the

control of BRD in the field, gamithromycin may offer prolonged protection against subsequent challenge by virulent bacteria.

Natural outbreaks of BRD commonly comprise infections with a number of different bacterial and viral pathogens, so it is useful to consider these results in relation to data generated in commercial farming operations. When gamithromycin was administered to in-contact animals after clinical BRD had been diagnosed in cattle within the same air space (metaphylaxis) in preregistration field trials, a high level of preventive efficacy was demonstrated. Evaluations were conducted over a 14-day posttreatment period, and 86% of treated animals remained clinically normal, while 39% of the saline-treated controls developed BRD (D. Baggott et al., submitted for publication). Postlaunch field studies of commercial feedlots in Europe provided additional evidence for the preventive or metaphylactic activity of gamithromycin following a single treatment (7, 23). Finally, the persistence of bactericidal concentrations in the lungs of calves following treatment of clinical disease is important in helping keep bacterial loads low in the affected lungs to allow the resolution of pathology and subsequent healing of the lungs to take place. A high therapeutic efficacy following a single administration of gamithromycin was observed previously in field trials in which calves naturally affected by BRD were treated (7, 23).

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