Demonstration of the metaphylactic use of gamithromycin against bacterial pathogens associated with bovine respiratory disease in a multicentre farm trial

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Context
The morbidity and mortality caused by bovine respiratory disease (BRD) is largely due to colonisation of the respiratory tract by pathogenic bacteria such as Mannheimia haemolytica, Pasteurella multocida and Histophilus somni and Mycoplasma species. The foundations of BRD control are sympathetic husbandry and appropriate vaccination, supported by the strategic or tactical use of antibiotics.

Gamithromycin, a macrolide of the azalide subclass, was recently developed exclusively for veterinary use as a single-dose, subcutaneous injectable solution (Zactran; Merial) for the therapeutic and preventive control of BRD associated with *M haemolytica*, *P multocida* and *H somni*.

Main conclusion
In a European multicentre field trial, described in this paper, gamithromycin given metaphylactically to cattle at high risk of developing BRD associated with *M haemolytica*, *P multocida* and/or *M bovis* was effective in reducing the morbidity of bacterial BRD.

Approach
Five commercial cattle rearing units in France, Germany and Italy were included in the trial. A total of 802 ruminating and younger, preruminating cattle were enrolled. At the time of enrolment, all animals included were considered healthy but at a high risk of BRD on the basis of the presence of at least 10 (equivalent to 5 per cent) or more of the cattle within the same airspace at each site having presented with clinical signs of BRD. The BRD pathogens *M haemolytica*, *P multocida* and/or *M bovis* were confirmed to be present in the trial populations by culture of nasal swabs collected before enrolment from animals confirmed with BRD within the airspace. Continuous exposure of the enrolled animals to BRD pathogens was ensured throughout the trial by the presence of target pathogen carriers in the form of saline-treated controls and non-enrolled peers maintained in the same airspace as the gamithromycin-treated cattle.

Half of the enrolled cattle were treated with 150 mg/ml gamithromycin solution at 6 mg/kg bodyweight and the other half received sterile 0.9 per cent saline solution at 2 ml/kg bodyweight as the control. Animals were observed daily from the day after treatment for 14 days for signs of BRD (defined as depression score $>0$ and respiratory character score $>0$ and rectal temperature $\geq 40.0^\circ C$); cattle that did not fulfil all the BRD criteria were removed on welfare grounds at the discretion of the attending veterinarian when the severity of their condition required immediate further treatment. On day 14, a treatment success was declared for cattle that had not been diagnosed with BRD.

For each individual site and all sites combined, the proportion of treatment successes on day 14 was compared between the gamithromycin-treated group and the controls using a two-sided significance level of 0.05 for all analyses.

Results
The proportion of metaphylactic preventive treatment successes, defined as the number of cattle surviving to day 14 without signs of BRD, in the gamithromycin-treated group (86 per cent) was significantly ($p=0.0012$) higher than in the saline-treated controls (61 per cent). Morbidity in the treated animals was reduced by 64 per cent compared with the controls.

Interpretation
The field trial involved a metaphylactic approach to the control of BRD, defined as the administration of an antibiotic to cohorts of apparently healthy animals that are in contact with clinical cases. The decision by a veterinarian to adopt a metaphylactic approach to the control of BRD rests on numerous considerations: one of the most important is the welfare of the animals. A therapeutic approach will generally result in a lower level of antibiotic usage, but this requires a high level of stockmanship in order to detect BRD in its early stages, and adequate labour and facilities with which to handle, examine and treat the affected animals promptly if their welfare is not to be compromised.

In this trial, which employed a metaphylactic approach, the risk of BRD was based on 5 per cent or more of the cattle within the airspace having presented with clinical signs of BRD after assembly and/or commingling at the trial site. This resulted in actual morbidity rates of 28 to 72 per cent among the controls. Treatment with gamithromycin significantly reduced morbidity by 64 per cent overall (32 to 62 per cent at individual sites), confirming that the predicted consequences of not treating in terms of morbidity among the untreated animals justified the use of the product by improving the welfare of the animals.

Part of the rationale for responsible use of antimicrobials is to limit the exposure of bacteria to sublethal levels of antibiotics in order to reduce selection for antibiotic resistance. The pharmacokinetic/pharmacodynamic profile of azalides such as gamithromycin is unique: high tissue concentrations, rapid accumulation in tissues, retention by macrophages and circulating phagocytes, long elimination half-life and prolonged postantibiotic effect. These properties of azalides, which are particularly enhanced for gamithromycin, coupled with appropriate use, reduce the potential for development of resistance against this subclass more than for many other antibiotic classes used in veterinary medicine.

Significance of findings
This European multicentre field trial has shown that gamithromycin, administered as a single treatment using a metaphylactic approach, is an effective tool in the control of BRD in at-risk cattle kept under a wide range of commercial conditions, and that such use is consistent with the responsible use of antibiotics in farm animals.
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