Attempts to integrate the pharmacokinetics of tiamulin (Denagard® - Novartis) in plasma with tiamulin MICs against Actinobacillus pleuropneumoniae (App) have proven ineffective, despite good clinical and microbiological responses to treatment. The purpose of this study was to determine MICs and MBCs of tiamulin against App and whether these would be consistently reduced by culturing the organism in 100% swine serum.

INTRODUCTION

Attempts to integrate the pharmacokinetics (PK) of tiamulin (Denargard® - Novartis Animal Health Inc.) concentrations in plasma with the pharmacodynamics (PD) measured as Minimum Inhibitory Concentration (MIC) against Actinobacillus pleuropneumoniae (App); using standardized MIC determinations, have been unsuccessful and led to considerations that lung ′′-′′ leucocyte concentrations might play a significant role, as estimated intracellular concentrations were 8.5µg/ml but only 0.47µg/ml in plasma (ratio 18:1). This is considered unjustifiable by some authorities as the infectious agent resides outside the cell in the extracellular compartment. Moreover, serum/plasma concentrations are better established for pharmacokinetic integration for most antibiotics. However, in an artificial infection study, an App isolate with a tiamulin MIC of 4µg/ml was effectively treated, both clinically and bacteriologically, with 180 ppm tiamulin in the drinking water. Studies using 2.5µg/ml in the culture media and 100% serum MICs reduced by 32 fold in the presence of serum. It was the purpose of this study to determine whether the MIC and Minimum Bactericidal Concentration (MBC) of tiamulin against App would be consistently reduced by culturing the organism in 100% swine serum in comparison with those achieved in serum-free culture medium.

MATERIALS AND METHODS

Tiamulin activity was measured against 19 UK field isolates (collected 2003-2009) and one type strain (ATCC 27090). Broth microdilution MIC/MBC tests were performed in accordance with CLSI guideline M31-A3, using Veterinary Fastidious Medium (VFM) - MHB, 5% lysed horse blood, yeast extract & yeast concentrate supplement, without serum (exact CLSI medium). For precision, a modified overlapping doubling dilution procedure was employed for MIC/MBC determination. Growth of App isolates grown in VFM was in accordance with previous surveys. The mean MIC and MBC plateau in 100% swine serum. MIC plates were incubated in 5% CO2 for 24-48h. MIC of App grown in VFM was in accordance with previous surveys. The mean MIC and MBC plateau in 100% swine serum. MIC plates were incubated in 5% CO2 for 24-48h.

RESULTS

The MIC and MBC results for 19 field isolates and the reference strain were determined following growth in VFM. Only 3 field isolates and the reference strain grew in 100% serum and there was no reduction in MIC.

DISCUSSION

Growth of App isolates was poor in 100% serum but the MICs were not reduced as previously observed with 50% serum. The MICs of the isolates grown in VFM were in accordance with previous surveys. The mean MIC was only 1.74 times the MIC for tiamulin against App, which is surprising as it is considered primarily a bacteriostatic antibiotic. This is in accordance with its clinical response but does not clarify the relationship between plasma concentrations and MIC/MBC.