Dose optimization of tiamulin (Denagard®) for the metaphylaxis and treatment of *Mycoplasma gallisepticum* infections in chickens

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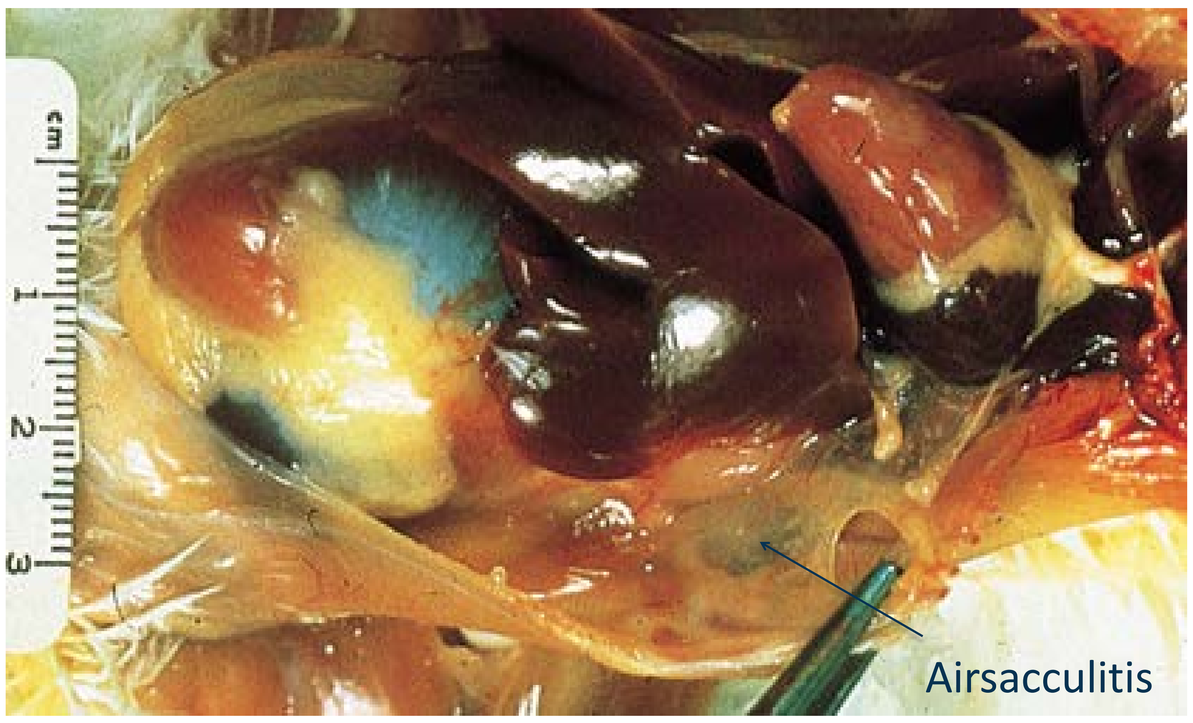
INTRODUCTION

Dose optimization or prediction (1, 2) is becoming an important aspect of pharmacokinetic (PK) and pharmacodynamic (PD) integration for an antimicrobial product to help achieve successful therapy. However, much of the work and standards have been carried out using bactericidal products such as the fluoroquinolones and aminoglycosides and therefore has some limitations when it comes to antibiotics primarily with a bacteriostatic mode of action. Tiamulin (Denagard® - Elanco), a pleuromutilin antibiotic is very active in vitro against *Mycoplasma gallisepticum* (MG) but can be considered primarily a bacteriostatic drug. It is the purpose of this paper to explore the limitations of this PK/PD approach in contrast to clinical evaluation.

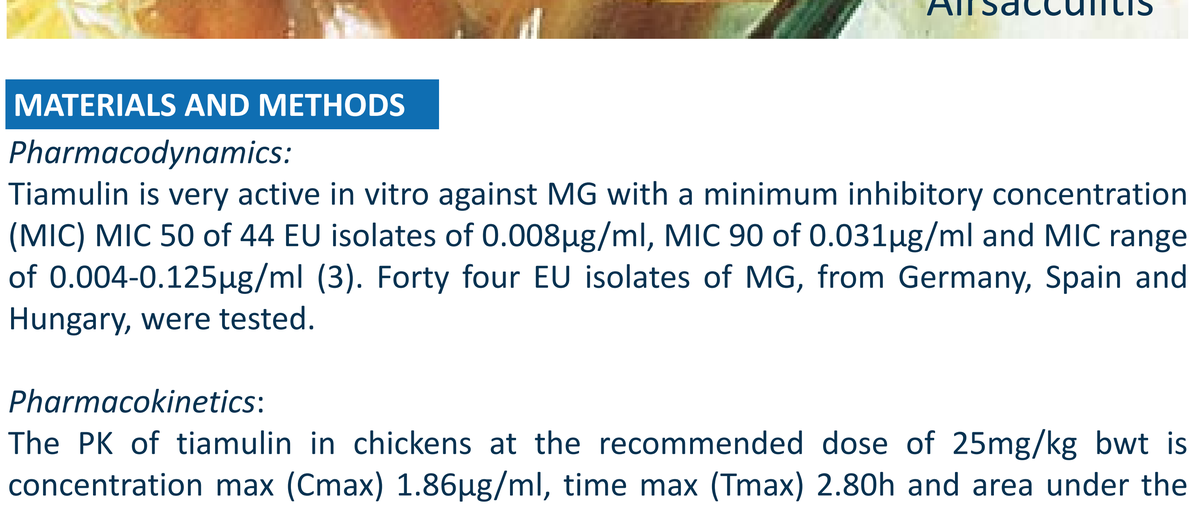


MATERIALS AND METHODS

Pharmacodynamics:
Tiamulin is very active in vitro against MG with a minimum inhibitory concentration (MIC) MIC 50 of 44 EU isolates of 0.008µg/ml, MIC 90 of 0.031µg/ml and MIC range of 0.004-0.125µg/ml (3). Forty four EU isolates of MG, from Germany, Spain and Hungary, were tested.

Pharmacokinetics:
The PK of tiamulin in chickens at the recommended dose of 25mg/kg bwt is concentration max (Cmax) 1.86µg/ml, time max (Tmax) 2.80h and area under the curve (AUC) 0-24h of 13.72µg.h/ml (4). However, after a deduction of 45% for plasma protein binding (PPB) the AUC becomes 7.55µg.h/ml, steady state concentration (Css) 0.31µg/ml and estimated clearance is 2.98(L/h/kg).

Fig 1. PK/PD relationships for tiamulin in plasma against MICs of 44 EU isolates of MG



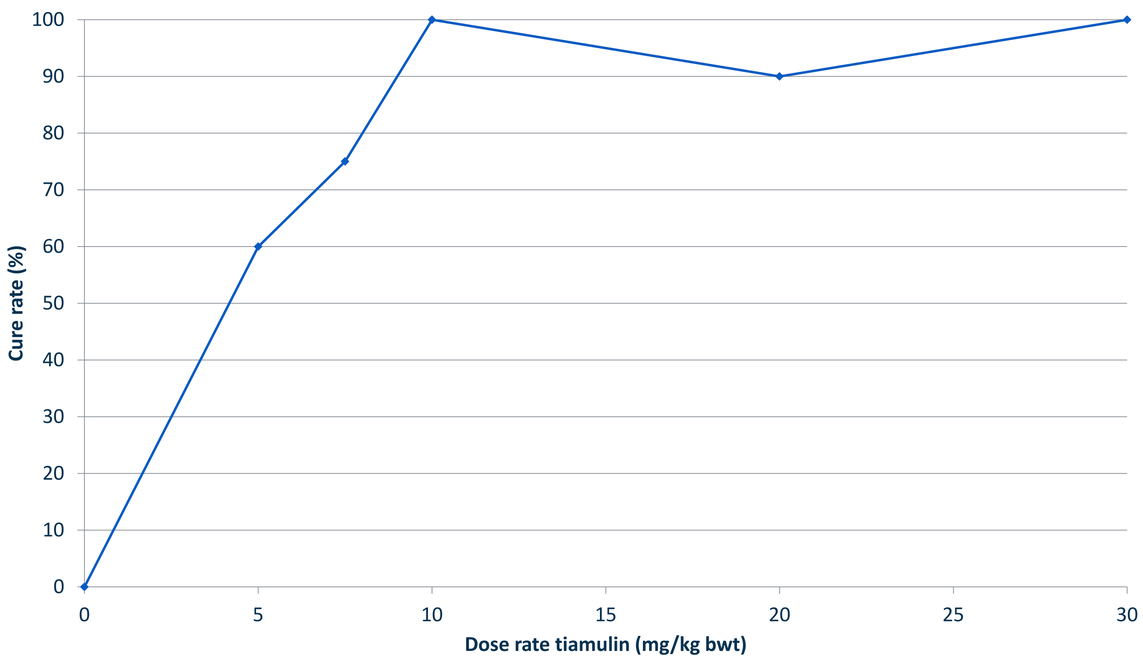
Dose rate calculations:
To calculate the optimum dose (OD) of tiamulin, the clearance (CL) is multiplied by the breakpoint index (BPI) (AUC/MIC h) usually 125h for bactericidal antibiotics (5) and multiplied by the targeted plasma concentration (TPC), which is the MIC 90 and divided by the bioavailability of the drug, which is 0.9 (90%).

$$OD\ (mg/kg) = \frac{CL\ 2.98L/h/kg \times BPI\ (AUC/MIC)\ 125h \times TPC\ (MIC90)\ 0.031\mu g/ml}{Bioavailability\ 0.9\ (90\%)}$$

On this basis the optimal dose for tiamulin was calculated at **12.8mg/kg bwt**.

Clinical assessment:
In an early dose-titration study (6) oral dosing of tiamulin was used for the early treatment (metaphylaxis/control) of an artificial infection with MG injected into the left air sac of 3 week old chicks. Chicks were treated for 3 days and then monitored for a further 5 days before necropsy. Efficacy (cure rate %) was judged by the absence of air sac lesions and the failure to re-isolate MG from the air sacs (see Figure 2).

Fig 2: Dose-titration effect of tiamulin administered orally for 3 days against MG (6)



A tiamulin dose of **10mg/kg bwt** and above gave a 90-100% eliminatory effect. The tiamulin MIC of the strain of MG used in the study was 0.0039µg/ml.

RESULTS AND DISCUSSIONS

On the face of it, the calculated dosage of 12.8mg tiamulin/kg bwt is similar to the clinical effect dose of 10mg tiamulin and above/kg bwt. However, in the calculation the tiamulin MIC 90 figure for MG of 0.031µg/ml was used and in the clinical study the MIC of the challenge strain was 0.0039µg/ml, approximately the MIC 50 and the BPI would be 774h not the 125h used as a standard for bactericidal drugs, approximately a 6 fold difference.
The minimum bactericidal concentration (MBC) might be a better parameter to use than the MIC.
This work demonstrates some of the limitations of fixed extrapolations when trying to apply them to bacteriostatic antibiotics in comparison with bactericidal drugs. It is better to combine both PK/PD extrapolations with clinical effect results, rather than depend on just PK/PD extrapolations.
Of particular interest, it also highlights the benefits of early treatment/metaphylaxis of Mycoplasma infections with tiamulin, as delayed treatments were not so effective (6).

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