PK/PD RELATIONSHIPS OF TETRACYCLINE (TETSOL®) ADMINISTERED IN MILK REPLACER AGAINST BOVINE RESPIRATORY PATHOGENS

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INTRODUCTION

Recently, there has been an increased interest in the use of tetracycline (Tetsol® – Novartis) in calves for the treatment of respiratory infections, in the UK, under 'cascade'. In the US, tetracycline is recommended for use at 20mg/kg bodyweight for the treatment of both enteric and respiratory infections[1]. On review of the literature, a variety of doses have been examined up to 50mg/kg bwt[2], especially for use in milk replacer. Concern has been expressed about the influence of calcium complexing with the drug and reducing the drug's bioavailability. It was the purpose of this paper to review the available pharmacokinetic (PK) data and compare it with recent pharmacodynamic (PD) data to establish a suitable dosage recommendation for the treatment of calf respiratory disease.

MATERIALS & METHODS

Tetracycline was administered at 50mg/kg bwt to one month old calves (Swedish red and white breed)[2]. The milk replacer containing the tetracycline was administered as the first morning feed. Blood samples were taken at 0, 1, 2, 4, 6, 8, 10 & 24h post dosing. In a second PK trial[2], tetracycline was administered twice daily at 25mg/kg bwt in two milk replacer feeds at 8 hours apart for 5 days. Blood samples were taken on day 1 at 2, 4, 8 & 10h and on day 5 at 2, 4, 10 & 12h. The tetracycline was assayed using a fluorometric, chemical assay[3] with an 89% recovery from serum. The minimum inhibitory concentration (MIC) work for *Pasteurella multocida* (*Pm*) (n=105) and *Mannheimia haemolytica* (*Mh*) (n=82)[4] was carried out using EU isolates, *Histophilus somni* (*Hs*) (n=80) Danish isolates[5] and *Mycoplasma bovis* (*Mb*) (n=35) isolates from Israeli and imported cattle[6]. The serum concentrations of tetracycline were modelled for a twice daily administration. The serum protein binding for tetracycline was reported at 31.6-41.4% depending on method.

RESULTS

In the first trial[2], the tetracycline C_{max} was 3.41µg/ml, the T_{max} was 4h, the AUC24h 34.14µg.h/ml and the Css could be estimated at 1.42µg/ml following the 50mg/kg bwt administration. When modelled for twice daily administration the concentration ranged between 0.83-2.28µg/ml and in the second PK trial[2] the figures were reported to be similar, between 1.35-2.25µg/ml. The serum Css, less serum protein binding of 41.4%[7], was 0.83µg/ml. The MIC_{50} for *P. multocida* was 0.5µg/ml, *M. haemolytica* 1.0µg/ml and *H. somni* and *M. bovis* 2.0µg/ml (see Figure 1)

CONCLUSIONS & DISCUSSION

Based on the PK trials[2], the modelling of serum concentrations at 25mg/kg twice daily was predictive of the actual results achieved. Tetracycline, administered in milk replacer twice daily, should be able to inhibit *P. multocida* effectively at the MIC_{50} level and nearly *M. haemolytica*. The serum concentrations would appear to be struggling to reach the MIC_{50} against *H. somni* and *M. bovis* (see Figure 2). Other authors[8] have demonstrated much higher serum concentrations of tetracycline in veal calves (Red Holstein/Simmental), also administered in milk at the same dose rate but using a microbiological assay method. A C_{max} of 8.2µg/ml, an AUC 24h of 123.2µg.h/ml and Css of 5.13µg/ml could be calculated from the results, which are substantially higher than in the Luthman *et al*., (1989) trials[2]. The apparent reason for the difference, whether breed, drug administration or method of analysis is currently unclear but would suggest that 50mg tetracycline/kg bwt given in milk would be sufficient to treat most 'wild type' calf respiratory pathogens.

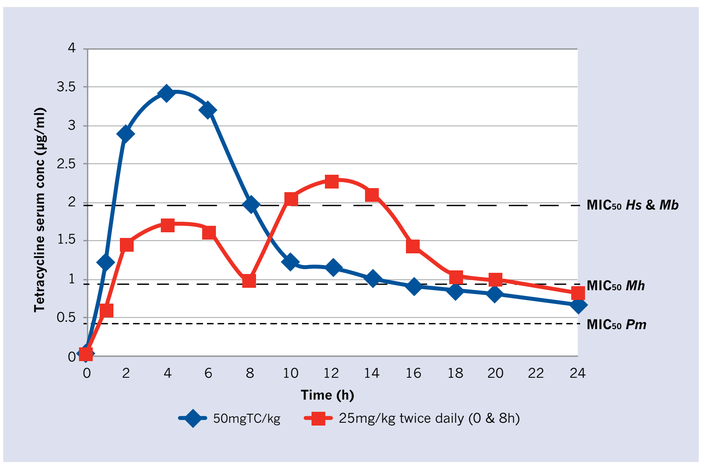

Figure 1. Comparison of tetracycline serum concentrations actual[2] and modelled with MIC_{50}s

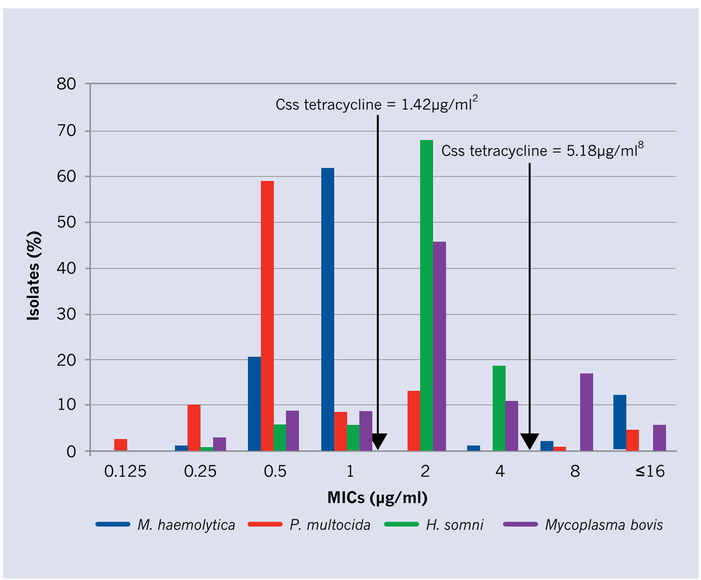

Figure 2. Comparison of tetracycline Css[2,8] and MICs of calf respiratory pathogens

Photo 1. Calf pneumonia – *Mycoplasma bovis* (From Currin *et al.*, 2009)

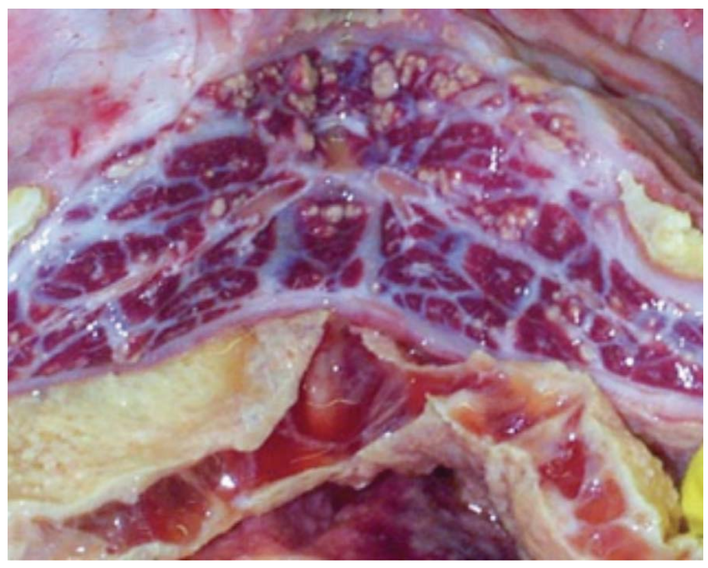

Photo 2. Calf pneumonia – *Mycoplasma bovis* (From Currin *et al.*, 2009)

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