

PK/PD integration of tiamulin (Denagard®) by injection against mycoplasmal infections of the lung and joints

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Introduction

Most of the work to develop effective dose rates of tiamulin injection (Denagard® – Novartis AH Inc.) for the treatment of enzootic pneumonia (*Mycoplasma hyopneumoniae* (MHP)) and mycoplasmal arthritis (*M. hyosynoviae* (MHS) and *M. hyorhinis* (MHR)) were carried out before the use of integration of the pharmacokinetics (PK) of tiamulin in plasma or joint fluid with the pharmacodynamics (PD) or minimum inhibitory concentration (MIC) of the various mycoplasmas involved was established. The purpose of this work was to review, retrospectively, the current PK /PD information and integration of tiamulin injection for these diseases.

Materials and method

Pharmacodynamics: Tiamulin's activity against a variety of swine pathogenic mycoplasma (Hannan et al, 1997) is summarised in Table 1.

Table 1. Susceptibility of various mycoplasma strains to tiamulin (µg/ml)

Species	No isolates	MIC 50	MIC 90	MIC range
MHP	20	0.05	0.05	0.01-0.1
MHS	18	0.005	0.025	0.0025-0.1
MHR	20	0.1	0.25	0.025-0.5

Hannan & Windsor (1998) showed that the minimum bactericidal concentration (MBC) was approximately 4 times the MIC for MHP and Goodwin (1985) described it as 2 for MHS and 1 for MHR.

Pharmacokinetics: Tiamulin is co-dependent on time and concentration to exert its mycoplasmacidal effect and therefore the area under the curve over 24h (AUC 24h) is the most suitable PK parameter to determine the potential anti-mycoplasmal effect. McKellar et al (1993 & 2004) demonstrated that the AUC 24h for tiamulin in plasma was 8.79µg.h/ml following an injection at 15mg/kg bodyweight. Combined data from McKellar et al (1993) and Skov & Nielsen (1988) showed that there was an average joint fluid concentration at 40% of the plasma concentration (range 28-59%) giving an AUC 24h of 3.52µg.h/ml.

Results and discussion

The results are summarised in Table 2.

Table 2. PK/PD integration for tiamulin using AUC24h / MBC (= MIC x MBC/MIC ratio)

Species	AUC 24h	MBC 50	MBC 90	AUC/ MBC 50	AUC/ MBC 90
MHP	8.79*	0.2	0.2	44	44
MHS	3.52**	0.01	0.05	352	70
MHR	3.52**	0.1	0.25	35	14

Key: * = AUC plasma; ** = AUC joint fluid

Using the ≥ 100 AUC/MIC (= MBC) ratio for bactericidal antimicrobials (Toutain, 2003) and ≥ 24 AUC/MIC ratio for bacteriostatic inhibitory antibiotics, tiamulin injection would appear to exert primarily an inhibitory effect at a dose of 15mg/kg bwt against MHP and MHR at both their MBC 50s and the former's MBC 90, but a strong mycoplasmacidal effect against MHS's MBC 50 and a likely mycoplasmacidal effect at its MBC 90. This was confirmed clinically by Burch & Goodwin (1984), markedly reducing lameness caused by MHS. Burch (1984) showed an inhibitory effect against MHP reducing lung lesions by 49% and Talummuk et al (2010) demonstrated marked joint swelling reduction in nursery pigs affected by MHR polyarthritis, following treatment with Denagard Injection.

References

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