PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS OF TIAMULIN (DENAGARD®) FOR RESPIRATORY INFECTIONS IN PIGS

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Introduction

The use of antimicrobial pharmacokinetic (PK) and pharmacodynamic (PD) relationships and their clinical effects are increasingly being used to better understand their mode of action, to improve dosing regimes and clinical efficacy. The pleuromutilin antibiotic tiamulin (Denagard® - Novartis Animal Health) when given to pigs via the drinking water will be used as an example, to demonstrate the PK/PD relationship for two contrasting respiratory infections caused by *Mycoplasma hyopneumoniae* (Mhp) and *Actinobacillus pleuropneumoniae* (App).

Material and Methods

A) Pharmacokinetics (PK)

Anderson et al, (1994) reported on the concentrations of tiamulin (THF) found in the lung following treatment with 60, 120 and 180ppm THF in the drinking water for 5 consecutive days. THF levels in blood were not recorded. To overcome this, a model was used, based on the data from McKellar et al (2004), where the area under the curve (AUC) was measured for both lung and plasma. An AUC lung: plasma ratio of 18.1: 1 was reported. This figure was used to estimate the rolling plasma levels from the lung concentrations in the former study (see Table 1).

Table 1: PK – concentration of THF in the lung and estimation for plasma (lung conc / 18.1)

THF (ppm) in water	Dose THF (mg/kg bwt)	Lung conc (µg/g)	Plasma conc (µg/ml)
60	6.16	1.11	0.061
120	13.2	4.26	0.235
180	20.9	8.50	0.470

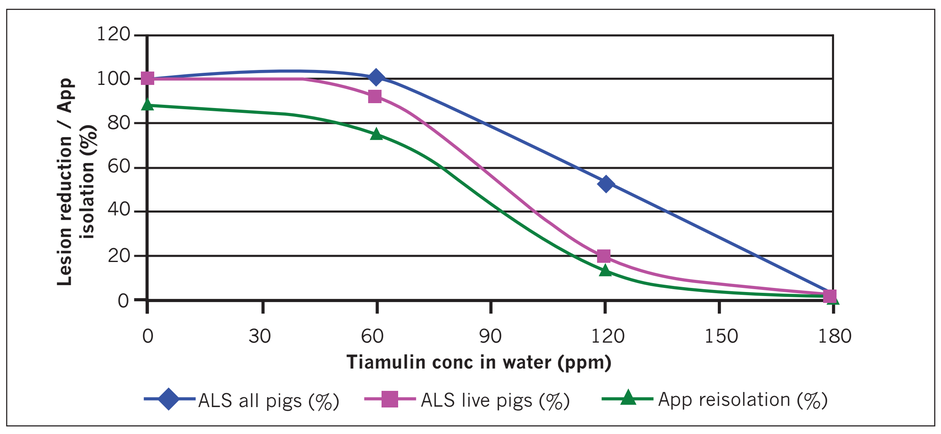
B) Pharmacodynamics (PD)

A recent report (Vicca et al, 2004) showed tiamulin to be highly active in vitro against 21 Belgian isolates of *M. hyopneumoniae* and a recent survey by Vetpath (2006) on 91 European isolates of *A. pleuropneumoniae* showed a very different susceptibility pattern (see Table 2).

Table 2: Comparison of tiamulin activity (MICs - (µg/ml)) against Mhp and App

Organism	MIC_{50}	MIC_{90}	Range
Mhp	0.03	0.12	≤ 0.015-0.12
App	4.0	8.0	1.0-1.6

Figure 1. Dose efficacy relationship with tiamulin against APP



C) Clinical effect

Mhp – Trial 1. An artificial infection study was carried out in gnotobiotic piglets (Underdahl and Szanto, 1976). Seven days after infection they were treated with tiamulin in milk at 8.8 and 17.6mg/kg bwt/day for 5 days. After a further 9 days the pigs were sacrificed. Trial 2. In Hannan et al (1982) tiamulin was dosed orally at 10mg/kg bwt twice daily for 10 days to pigs 14 days after infection and they were sacrificed 14 days after treatment. The MIC for the isolates used was 0.1µg/ml
(see Table 3).

Table 3: Challenge study with THF (mg/kg bwt/day) against Mhp – average lung score (ALS)

Trial	THF 0	THF 8.8	THF 17.6	THF 20
1	100%	100%	21%	-
2a	100%	-	-	22%
2b	100%	-	-	2%

App – Shultz and Anderson (1983) infected pigs intranasally with App ST 5 with a MIC of 4µg/ml. At the first signs of clinical pneumonia they were treated with THF at 0, 60, 120 & 180ppm for 5 days in the drinking water. The surviving pigs were necropsied at 21 days after infection, (see Table 4 & Figure 1).

Table 4: Challenge study with THF against App

THF (ppm) in water	Mortality (24 hrs)	ALS	ALS (live pigs)	App isolation
0	2/8	100%	100%	7/8
60	1/8	100%	92%	6/8
120	1/8	52%	19%	1/8
180	0/8	2%	2%	0/8

Results and conclusions

Mhp – there was a good correlation between estimated **plasma** levels, MICs and clinical effect.

App – in contrast, there was a good correlation between **lung** concentrations, MICs and clinical effect. Tiamulin is primarily bacteriostatic in effect. Studies prove the marked effect of Denagard against Mhp/App infections and PK/PD analysis is an effective tool to explain the actions of antibiotics like Denagard.

References

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