Tiamulin (Denagard®) by injection – PK/PD relationships with \textit{M. hyorhinis} and \textit{M. hyopneumoniae}

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\textbf{Introduction}
Tiamulin by injection (Denagard® - Novartis AH Inc.) was shown to be particularly effective against \textit{Mycoplasma hyorhinis} (\textit{MHR}) associated arthritis in young growing swine, causing a marked reduction in swollen joints (1). An in-vitro microbiological study (2) showed that the minimum inhibitory concentrations (MICs) of tiamulin against both \textit{MHR} and \textit{M. hyopneumoniae} (\textit{MHP}) were very low. It was the purpose of this paper to look at the pharmacokinetic (PK) and pharmacodynamic (PD) relationships of tiamulin against mycoplasmal isolates from Thailand.

\textbf{Materials and methods}

\textit{Pharmacodynamics:} The MIC 50 and MIC 90 values for tiamulin against 20 recent Thai isolates of \textit{MHP} and \textit{MHR} were reported (2).

\textbf{Table 1.} Susceptibility of 20 recent Thai \textit{MHP} and \textit{MHR} isolates to tiamulin

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC 50 (µg/ml)</th>
<th>MIC 90 (µg/ml)</th>
<th>MIC range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHP</td>
<td>0.048</td>
<td>0.097</td>
<td>0.048-0.19</td>
</tr>
<tr>
<td>MHR</td>
<td>0.097</td>
<td>0.097</td>
<td>0.048-0.097</td>
</tr>
</tbody>
</table>

\textit{Pharmacokinetics:} Tiamulin distributes well into joint fluid after intramuscular administration. The concentrations achieved in plasma and joint fluid following an injection of Denagard 20% at 15mg/kg bodyweight was described (3, 4 & 5). Peak concentrations (Cmax) of tiamulin in plasma were recorded as 0.61µg/ml (4) and that, on average, concentrations in joint fluid were approximately 40% of plasma concentration (3 & 5) (Ref Figure 1).

\textbf{Results and discussion}
The correlation between plasma and joint fluid concentrations with the MIC 90 of \textit{MHP} and \textit{MHR} at 0.097µg/ml are highlighted in Figure 1.

\textbf{Fig 1.} Correlation of tiamulin PK in plasma and joint fluid and PD (MIC 90) against \textit{MHP} and \textit{MHR}

There is a good PK correlation with tiamulin concentrations in plasma exceeding the tiamulin MIC 90 for \textit{MHP} over a 24 hour period. The recommended treatment interval is 3 applications over 3 consecutive days. Tiamulin concentrations in joint fluid are somewhat lower, but appear to cover 21 hours of the 24 hour (87.5%) dosing period at the MIC 90 concentration. Many bacteriostatic antibiotics, which exert a concentration-related effect on the ribosome and thereby inhibit protein production, demonstrate a post-antibiotic effect (PAE) inhibiting bacterial re-growth for several hours (6) after plasma or tissue concentrations decline. This is likely to be the case for tiamulin against \textit{MHR}.

Denagard injection at 15mg/kg bwt correlates well with its indications for the treatment of both mycoplasmal pneumonia and arthritis.

\textbf{References}