PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIPS OF VALNEMULIN (ECONOR®) FOR PORCINE PROLIFERATIVE ENTEROPATHY ‘ILEITIS’

D.G.S. Burch1 and U. Klein2

1 Octagon Services Ltd, Old Windsor, Berks, UK 2 Novartis Animal Health Inc., Basel, Switzerland
d.burch@octagon-services.co.uk

Introduction
Valnemulin (Econor® - Novartis Animal Health), a pleuromutilin antibiotic with exceptional activity against gut pathogens Brachyspira hyodysenteriae and B. pilosicoli was reported to have activity against Lawsonia intracellularis (Li), (1) the causal agent of porcine proliferative enteropathy or ‘ileitis’. The intracellular minimum inhibitory concentration (MIC) was reported at <2.0µg/ml but it had not been titrated down further. Valnemulin (VAL) has been shown to be highly effective in the treatment of ileitis (1) when given in feed. It was the purpose of this paper to look at the pharmacokinetics (PK) of VAL in the gut contents and relate these to the pharmacodynamics (PD) of VAL and its clinical effect against L. intracellularis.

Material and Methods
A) Pharmacokinetics (PK)
VAL concentrations were described in colon contents following in feed medication at approximately 75 and 200 ppm for 28 days. The relationship between colon and ileal contents was modeled and it was estimated that an effective steady state concentration of approximately 29% of the colon contents was found in the ileum over a 12 hour period following a single feed application. This figure was used to determine the ileal contents concentration of VAL (see Figure 1).

B) Pharmacodynamics (PD)
A recent report (4) showed that VAL has a very low intracellular MIC 50 and MIC 90 against 10 isolates of Li from both Europe and the United States, at <0.125µg/ml. This level was much lower than previously reported (1) at <2µg/ml. The method was slightly different and used McCoy cells rather than rat enterocytes (IEC-18 cells) to grow the Li but they also used a wider range of dilutions than the original study, down to 0.125µg/ml.

C) Clinical effect
In an artificial challenge trial (3), VAL was given in feed at 25, 37.5 & 50 ppm, from 2 days before challenge with Li strain LR189/5/83, with an intracellular MIC of <0.125µg/ml, until termination 21 days after infection. In the treatment study (3), VAL was given 7 days after infection for 14 days until termination (see Table 1).

Table 1: Necropsy results (ileum) of the prevention (25, 37.5 & 50 ppm) and treatment trial (75 & 125 ppm)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gross lesions</th>
<th>Micro lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected control</td>
<td>5/7</td>
<td>6/7</td>
</tr>
<tr>
<td>VAL 25 ppm (P)</td>
<td>2/7</td>
<td>6/7</td>
</tr>
<tr>
<td>VAL 37.5 ppm (P)</td>
<td>1/5</td>
<td>2/5</td>
</tr>
<tr>
<td>VAL 50 ppm (P)</td>
<td>0/7</td>
<td>1/7</td>
</tr>
<tr>
<td>VAL 75 ppm (T)</td>
<td>0/7</td>
<td>0/7</td>
</tr>
<tr>
<td>VAL 125 ppm (T)</td>
<td>0/7</td>
<td>0/7</td>
</tr>
</tbody>
</table>

Results and conclusions
The results show that effective concentrations of VAL are achieved in the ileal contents and these are sufficient to inhibit the development of gross lesions of ileitis at 50 ppm VAL in feed and also to treat and eliminate the infection at 75 ppm VAL and above (see Figure 2 & 3). This is approximately 3.9 times the MIC and equivalent to an AUC/MIC of 94.

References