PHARMACOKINETIC / PHARMACODYNAMIC (PK/PD) RELATIONSHIPS OF DENAGARD® (TIAMULIN) IN DRINKING WATER FOR THE TREATMENT OF ILEITIS

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Objectives:

The objective of the work was to compare the pharmacokinetics (PK) of the estimated tiamulin ileum contents concentration (ICC) and compare this with the intracellular minimum inhibitory concentrations (iMICs) against *Lawsonia intracellularis*, the cause of Porcine Proliferative Enteropathy (PPE) 'ileitis' (see Photo 1 and 2), derived from laboratory studies (pharmacodynamics - PD) and evaluate the clinical efficacy of the drug when administered in the drinking water in an artificial infection study.

Materials and methods:

The tiamulin ICC was estimated using a PK model (Burch, 2005) based on the tiamulin colonic contents concentration (CCC) recorded by Anderson et al (1994) following the administration of tiamulin (Denagard® – Novartis Animal Health Inc.) via the drinking water at 60ppm for 5 days and compared with the iMICs derived from Wattanaphansak et al (2009) against 10 EU and US isolates of *L. intracellularis*. The test was repeated twice. An artificial infection study was reported by Walter *et al.,* (2001) where pigs were infected with a pure culture of *L. intracellularis*. When one or more pigs in >60% of the pens were showing clinical signs of ileitis, the pigs were medicated with tiamulin at 60ppm via the drinking water for 5 days. There was a 10day observation period after which the pigs were necropsied.

Results:

The CCC was recorded at 2.16µg/g and the estimated ICC was calculated at 29% of the CCC = 0.63µg/g. The MIC 90 of tiamulin against *L. intracellularis* was ≤0.12µg/ml. The AUC/MIC was 126 and the time > MIC 90 was 100% (see Figure 1).
In the artificial infection study, the clinical signs almost disappeared by day 3 in the treated pigs (see Figure 2) and at necropsy the gross lesions in the ileum were significantly reduced from 50% in the untreated controls to 8% in the treated pigs and the microscopic lesions from 82% to 7%, respectively (see Figure 3).

Conclusions:

Using the ICC and the intracellular MIC of tiamulin appears to give a good correlation for the prediction of efficacy for the treatment of ileitis, when administered in the drinking water at 60ppm. This anticipated efficacy was confirmed in an artificial challenge study.

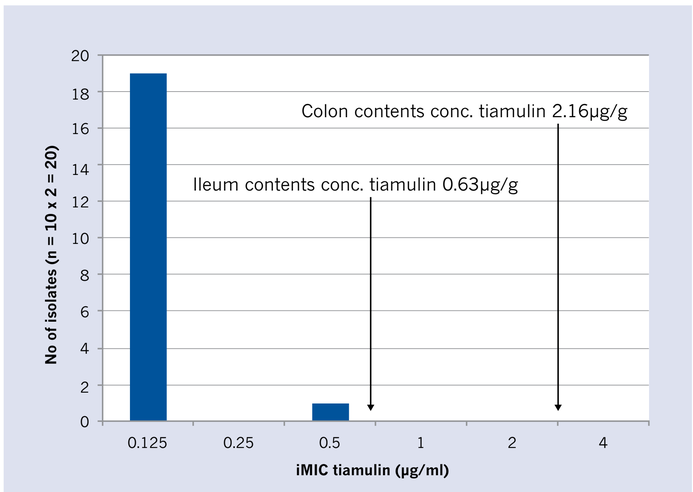

Figure 1. The relationship of ileum contents concentration (estimated) and iMICs of tiamulin against *L. intracellularis* (Wattanaphansak *et al.,* 2009)

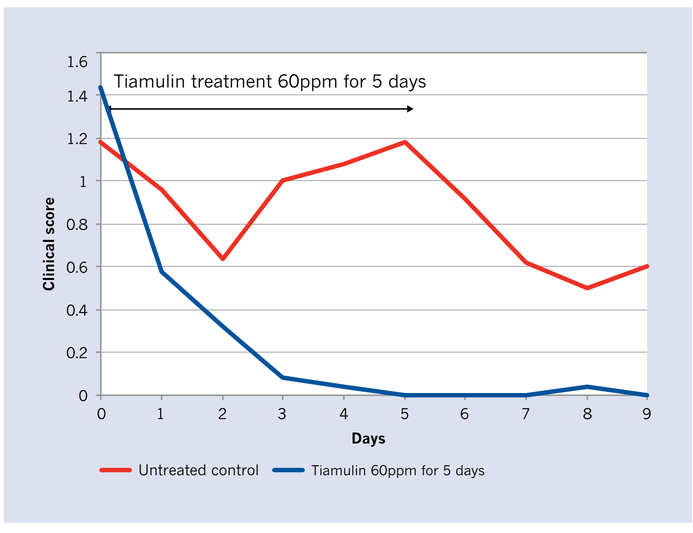

Figure 2. Clinical response to tiamulin in the drinking water against an artificial ileitis challenge (Walter *et al.,* 2001) – (MIC of the organism 0.25µg/ml)

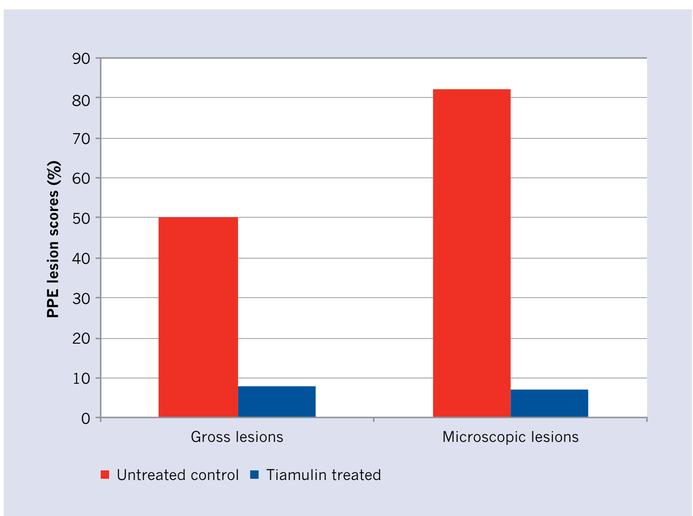

Figure 3. Effect of tiamulin on ileum lesion scores (Walter *et al.*, 2001)

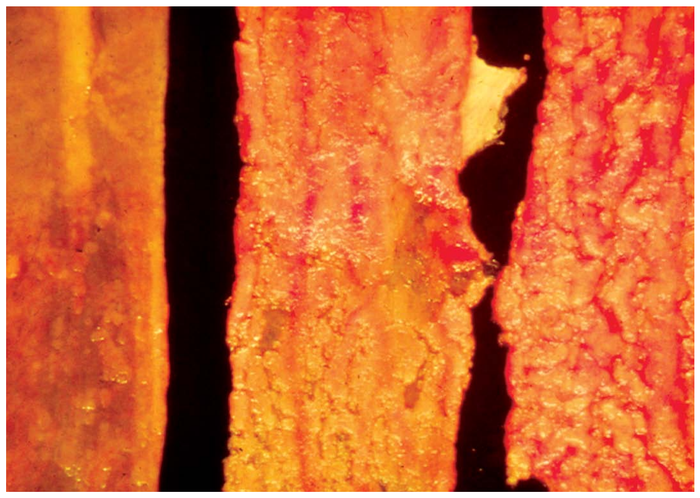

Photo 1. Thickening of the ileum associated with PPE – 'ileitis'

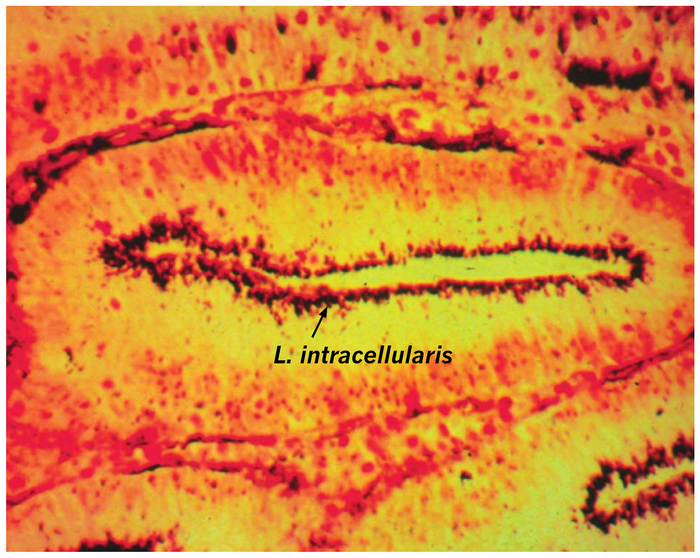

Photo 2. *Lawsonia intracellularis* colonising ileum epithelial cells

References:

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Burch, D. (2005) Pig Journal, 56, 25-44
Walter, D. *et al.,* (2001) J. Swine Health and Production, 9, 3, 109-115
Wattanaphansak, S. *et al.,* (2009) Vet Microbiology, 134, 305-310

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