# Pharmacokinetic / Pharmacodynamic Relationships of Valnemulin (Econor®) and *Lawsonia intracellularis* the Cause of 'Ileitis'

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## Introduction

Valnemulin (Econor® - Novartis Animal Health Inc.), a pleuromutilin with exceptional activity against the gut pathogens *Brachyspira hyodysenteriae* and *B. pilosicoli* was reported to have good activity against *Lawsonia intracellularis* (*Li*), (1) the causal agent of Porcine Proliferative Enteropathy or 'ileitis'. 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 *Li.*

## Materials and methods

*A) Pharmacokinetics (PK)*

VAL concentrations were described in colon contents (2) following in feed medication at approximately 75 and 200 ppm for 28 days at 1.6and 5.2µg/g. The relationship between colon and ileum contents was modelled (3) and it was estimated that an effective steady state concentration of approximately 29% of the colon contents was found in the ileum. These figures were used to determine the ileum contents concentration of VAL at 0.49 and 1.5µg/ml, respectively.

*B) Pharmacodynamics (PD)*

A recent report (4) showed that VAL had a very low intracellular MIC 90 against 10 isolates of *Li* from the United States (n=6) and Europe (n=4), at ≤0.125µg/ml. This level was much lower than previously reported (1) at <2µg/ml. The in vitro method was slightly different and used McCoy cells rather than rat enterocytes (IEC-18 cells) to grow the *Li*. They also used a wider range of different concentrations (0.125-128µg/ml) than the original study, making a titration of low and high MICs possible.

*C) Clinical effect*

In an artificial challenge trial (1), 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 challenge study (1), VAL was given 7 days after infection for 14 days until termination (see Table 1). Lesions in the ileum were examined grossly and histologically.

## Results and discussion

Effective concentrations of VAL are achieved in the ileum contents, which inhibited the development of gross lesions of ileitis at 50 ppm. At 75 ppm VAL and above, no gross or microscopic lesions were observed (see Figure 1 & 2) following treatment.

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

| Treatment | Gross lesions | Micro lesions |
|---|---|---|
| Infected control | 5/7 | 6/7 |
| VAL 25ppm (P) | 2/7 | 6/7 |
| VAL 37.5ppm (P) | 1/5 | 2/5 |
| VAL 50 ppm (P) | 0/7 | 1/7 |
| VAL 75ppm (T) | 0/7 | 0/7 |
| VAL 125 ppm (T) | 0/7 | 0/7 |

**Figure 1.** PK/PD relationship of VAL in ileum contents

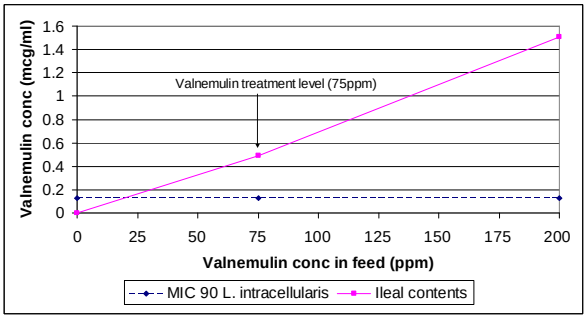
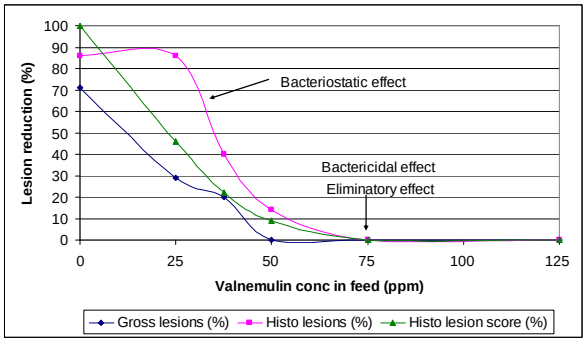



**Figure 2.** Dose/efficacy relationship with VAL in feed




## References

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