PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIPS OF TIAMULIN (DENAGARD®) FOR PROLIFERATIVE ENTEROPATHY 'ILEITIS'

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Introduction

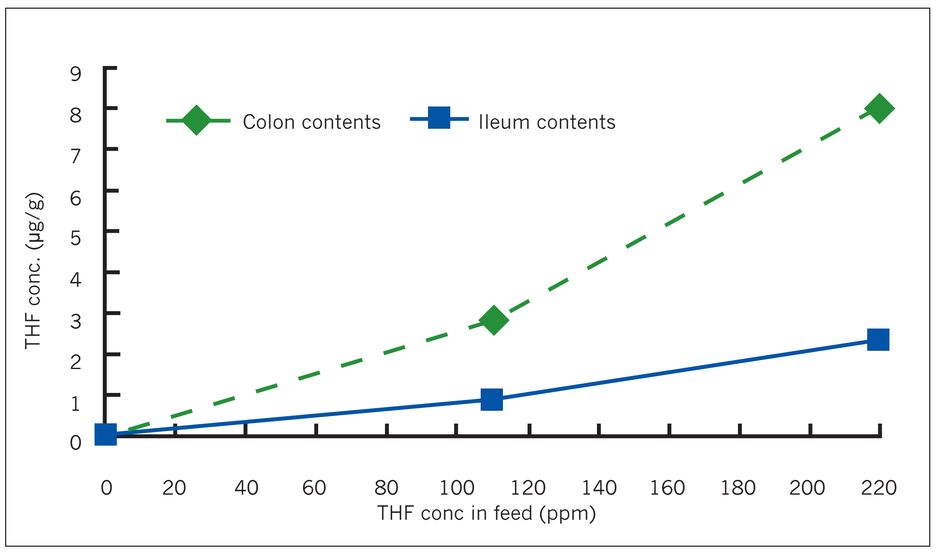
Tiamulin (Denagard® - Novartis Animal Health) has been shown to be highly active against *Lawsonia intracellularis* (Li), (1, 2) the causal agent and highly effective in the prevention and treatment of proliferative enteropathy or 'ileitis' (3) when given in feed. It was the purpose of this paper to look at the pharmacokinetics (PK) of tiamulin (THF) in the gut contents and relate these to the pharmacodynamics (PD) of tiamulin and its clinical effect against *L. intracellularis*.

Material and Methods

A) Pharmacokinetics (PK)

THF concentrations were described in colon contents (4) following in feed medication at 110 and 220 ppm for 14 days. The relationship between colon and ileal contents was modeled (5) and it was estimated that an effective concentration of approximately 29% of the colon contents was found in the ileum over a 12 hour period after a single feed application. This figure was used to determine the ileal contents concentration of THF (see Figure 1).

Figure 1. THF colon and estimated ileal contents concentration



B) Pharmacodynamics (PD)

A recent report (2) showed that THF 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 4µg/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 the prevention trial (3), Denagard was given in feed at 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), Denagard was given 7 days after infection for 14 days until termination (see Table 1). Both regimes were completely effective in reducing gross and microscopic lesions in ileum

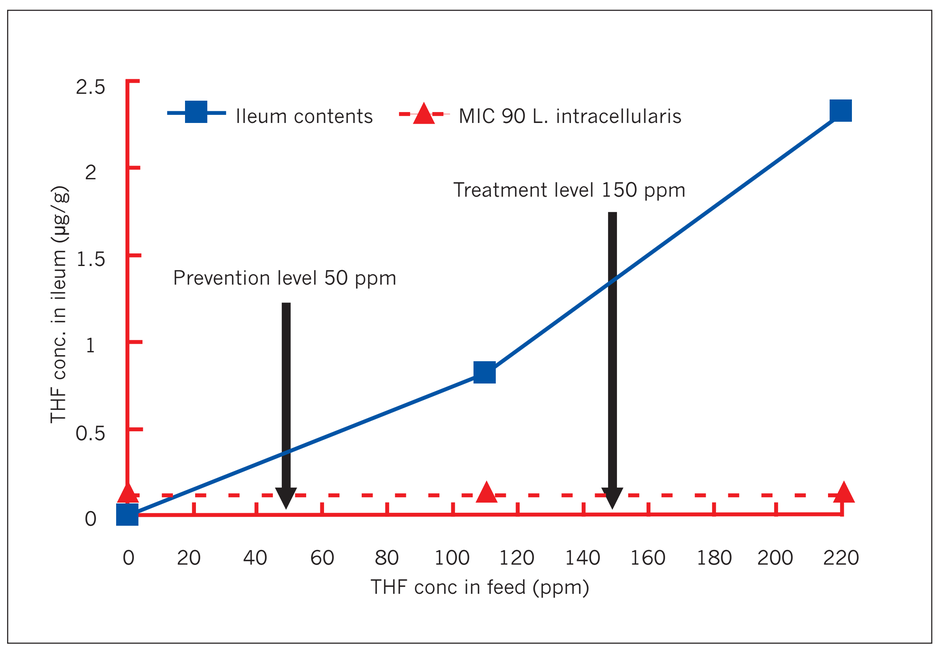
Table 1: Necropsy results (ileum) of the prevention (50 ppm) and treatment trial (150 ppm)

Treatment	Gross lesions	Micro lesions
Infected control	6/7	7/7
Dena 50 ppm (P)	0/6	0/6
Dena 150 ppm (T)	0/7	0/7

Results and conclusions

The results show that effective concentrations of THF are achieved in the ileal contents and these are sufficient to inhibit the development of ileitis at 50 ppm Denagard in feed and also to treat infections at 150 ppm Denagard completely (see Figure 2).

Figure 2. PK/PD relationship of THF in the ileal contents and Li MIC 90 of 0.125µg/ml



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