

Ileitis pharmacokinetics and pharmacodynamics

Issue

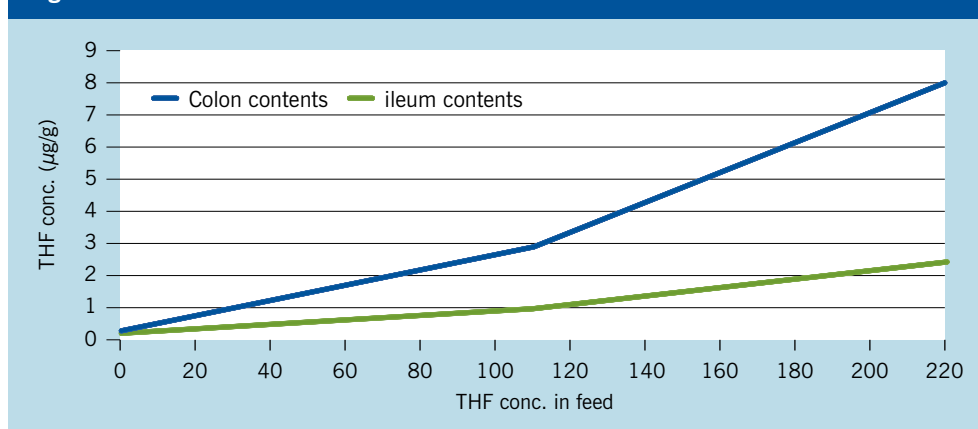
(PD) of antimicrobials are increasingly used to understand their mode of action and clinical efficacy. The pharmacokinetics of tiamulin hydrogen fumarate (THF, Denagard®) in the gut contents and the relationship to the pharmacodynamics and the clinical effect of Denagard against *Lawsonia intracellularis* are described in this paper.

Study

In a challenge study, the effect of Denagard Premix as a treatment (150ppm, commencing 7 days post infection) or as a preventive (50ppm, commencing 2 days pre-challenge and continuing for 21 days until the trial termination) was evaluated¹. All pigs receiving Denagard Premix at 50 and 150ppm before and after challenge, remained clinically normal, were free from diarrhoea and had no PE lesions at post mortem. The THF concentrations were described in the colon contents following in feed medication at 110 and 220 ppm for 14 days² and the relationship between the colon and ileal contents was modeled and estimated.³

Findings

Figure 1: Tiamulin colon and estimated ileal contents concentration



- Effective concentrations of tiamulin hydrogen fumarate (Denagard) are achieved in the ileal contents by in-feed medication (Figure 1)

Table 1: Necropsy results (ileum) at prevention (50ppm) and treatment (150ppm) dosage

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

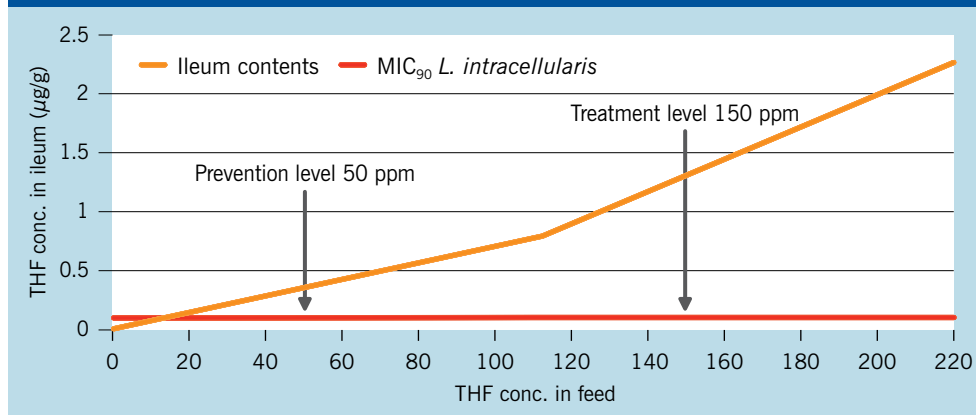
These concentrations are sufficient to inhibit the development of ileitis at 50ppm Denagard in feed and also to treat ileitis infections at 150ppm Denagard completely (Table 1).



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Figure 2: PK/PD relationship of THF in the ileal contents and *Li* MIC₉₀ of 0.125 µg/ml



- The pharmacokinetic (PK) and pharmacodynamic (PD) relationships of tiamulin hydrogen fumarate correlate well with its clinical activity against ileitis (Figure 2)

The substantial therapeutic effect of tiamulin (Denagard) can be explained by the gut pharmacokinetics and the high sensitivity of L. intracellularis strains to Denagard.

- Based on new MIC data, tiamulin is considered as the most active antimicrobial inhibiting the intracellular activity of all *L. intracellularis* isolates at <0.5 µg/ml. Extracellular activity results also confirm the highest sensitivity of *L. intracellularis* strains to tiamulin in comparison to other antimicrobials tested

A recent report⁴ shows the pronounced effect of Denagard against L. intracellularis in vitro. Very low intracellular MIC₅₀ and MIC₉₀ (0.125 µg/ml) against 10 strains of L. intracellularis isolated from Europe and the United States were found.

Conclusions

- Denagard is highly effective for the prevention and treatment of ileitis
- Denagard in-feed medication provides high THF concentrations in the ileum and colon
- The gut pharmacokinetics and pharmacodynamics of THF correlate well with its clinical activity against ileitis and these PK/PD relationships provide an effective tool to understand the ability of THF to inhibit *L. intracellularis* infections
- Low tiamulin MICs and narrow MIC ranges prove the high susceptibility of *L. intracellularis* strains (from Europe and the US) and the consistent efficacy of tiamulin against this pathogen

References:

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