NOVARTIS ANIMAL HEALTH

Pharmacokinetic/Pharmacodynamic relationships of Valnemulin for the prevention of Epizootic Rabbit Enteropathy

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Introduction: Epizootic rabbit enteropathy (ERE) is a complex gastrointestinal disorder of farmed rabbits aged between 6-14 weeks, usually occurring after weaning and is characterised by loss of appetite and mortality (1, 2), between 30-80% in untreated herds. Gross lesions include gross distension of the abdomen and dilatation of the stomach and small intestines with mainly liquid contents (see Photo 1) causing tympany and borborygmy. The caecum can be impacted or contains liquid and mucus may be found in the colon. The precise aetiology is unknown, however *Clostridium perfringens* seems to be the dominant pathogen associated with it (2) producing either A or C toxin types. There is usually no evidence of inflammation, if there is it may be associated with other enteric pathogens. Valnemulin (Econor® - Novartis Animal Health Inc.) has recently been approved for use against this disease at 35ppm in the feed for the *'reduction of mortality during an outbreak of epizootic rabbit enteropathy. Treatment should be started early in the outbreak, when the first rabbit has been diagnosed with the disease clinically.'*

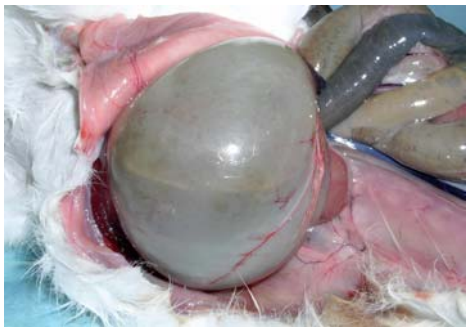


Photo 1: Distended abdominal contents of a rabbit with ERE

Materials & methods: *Pharmacokinetics (PK):* The concentration of valnemulin was determined in the caecal contents using a validated LC MS/MS method following administration of valnemulin for 35 days in feed at 60ppm (3).

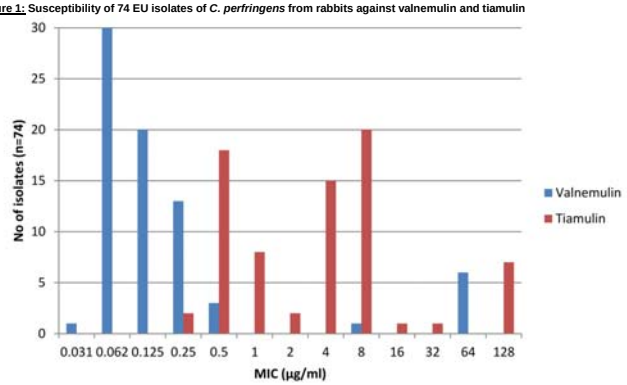
Pharmacodynamics (PD): The minimum inhibitory concentrations (MICs) of valnemulin and tiamulin were determined against 74 isolates of *C. perfringens* from Italy, France and Spain (4).

Clinical trials: A number of clinical trials were carried out. The first was for the prevention of ERE (5). Specific pathogen free (SPF) rabbits were artificially challenged with gut contents from previously clinically affected rabbits and concentrations of valnemulin at 0, 20, 35 and 60ppm in feed were tested. A second trial (6) was carried out in the field and was meant to be early treatment but due to the rapidity of onset of the clinical problem, it became a treatment study and an early treatment (metaphylaxis) study, of those with delayed onset. Valnemulin at 20, 35 and 60ppm was administered via the feed and compared with untreated controls. The third study (7) was primarily an early treatment field trial, when clinical signs of disease were just beginning, the rabbits were treated with 0, 20 and 35ppm valnemulin in the feed.

Results: *Pharmacokinetics:* The concentration of valnemulin in the caecal contents was 3.8µg/g at 60ppm, an estimated equivalent to 2.2µg/g for 35ppm and 1.3µg/g for 20ppm.

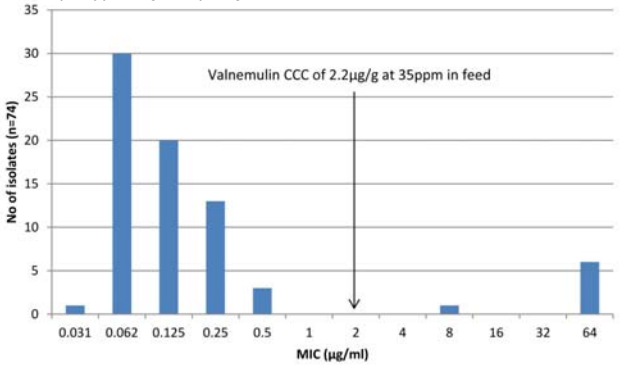
Pharmacodynamics: For valnemulin, the MIC 50 was 0.125µg/ml, MIC 90 was 0.5µg/ml and MIC range 0.031-64µg/ml; for tiamulin the MIC 50 was 4.0µg/ml, MIC 90 was 8.0µg/ml and MIC range 0.25-128µg/ml. Valnemulin demonstrated a very different pattern of susceptibility (monophasic) in comparison with tiamulin, which showed an apparent intermediate or biphasic susceptibility pattern (see Figure 1)

Figure 1: Susceptibility of 74 EU isolates of *C. perfringens* from rabbits against valnemulin and tiamulin



When the PK and PD of valnemulin were compared, inhibitory concentrations above the main susceptibility pattern would be achieved by the 20, 35 and 60ppm in feed inclusion levels in the caecal contents.

Figure 2: PK/PD relationship of valnemulin's caecal contents concentration (CCC) and susceptibility pattern against *C. perfringens*



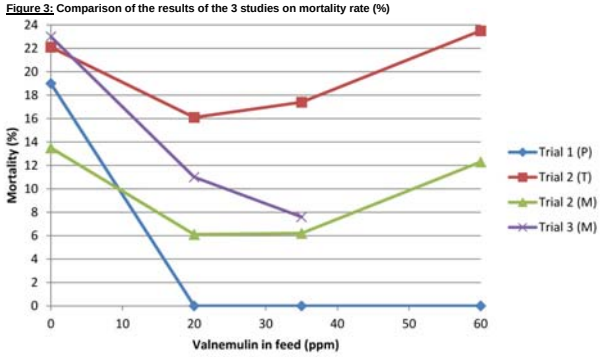
Clinical trials: In the first study, a prevention study, the rabbits were given the medication before infection and valnemulin completely prevented mortality associated with ERE although 19% of the untreated control rabbits died. In the second study, a treatment study, where the rabbits were breaking down with a natural infection there was little difference between the treated and untreated rabbits with a mortality of approximately 22%. In those rabbits that were not showing clinical signs when treatment started, mortality was halved to 6% in the 20 and 35ppm groups in comparison with the untreated controls showing a 14% mortality. In the third study, an early treatment or metaphylaxis study, the mortality in the 20 and 35ppm groups was 11 and 8%, respectively, which were significantly better than the untreated controls at 23% (see Table 1 and Figure 3).

Valnemulin (ppm)	0	20	35	60
Trial 1 (P)	19	0	0	0
Trial 2 (T)	22.1	16.1	17.4	23.5
Trial 2 (M)	13.5	6.1	6.2	12.3
Trial 3 (M)	23	11	7.6	-

Key: P = prevention; M = metaphylaxis or early treatment; T = treatment

Table 1: Comparison of the results of the 3 clinical studies on mortality rates (%)

Figure 3: Comparison of the results of the 3 studies on mortality rate (%)



Conclusion: Valnemulin is highly active against *C. perfringens*, and with a different susceptibility pattern in comparison with tiamulin. Valnemulin at 20ppm and above was highly effective in preventing ERE but the closer it was given to when the clinical disease was anticipated (metaphylaxis) or had actually started (treatment), a reduced efficacy against ERE was demonstrated. Interestingly, higher concentrations of valnemulin up to 60ppm did not reverse this effect. It is possible, due to the nature of the disease, by the time clinical signs are apparent, it is already too late to treat afflicted rabbits.

References: 1. Huybens, N. et al. (2011) Veterinary Journal, 190, 416-417. **2.** Marlier, D. et al. (2006) Veterinary Journal, 172 (3): 493-500. **3.** Karadzovska, D. (2009) Novartis report no. YO8/79/2240 **4.** Pridmore, A. (2011) Novartis report no. 041/06 reference AH5342 **5.** Licois, D. et al. (2008) Novartis report no. ECOFRA0107 **6.** Sarasola, P. (2011) Novartis report no. ESP-08-001 **7.** Adler and Radeloff (2012) Novartis report no. CH-12-010

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