PK/PD and clinical relationships of Pharmasin®/Tylovet® Premix (tylosin phosphate) administered to pigs for the treatment of Necrotic Enteritis

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Background and Objectives

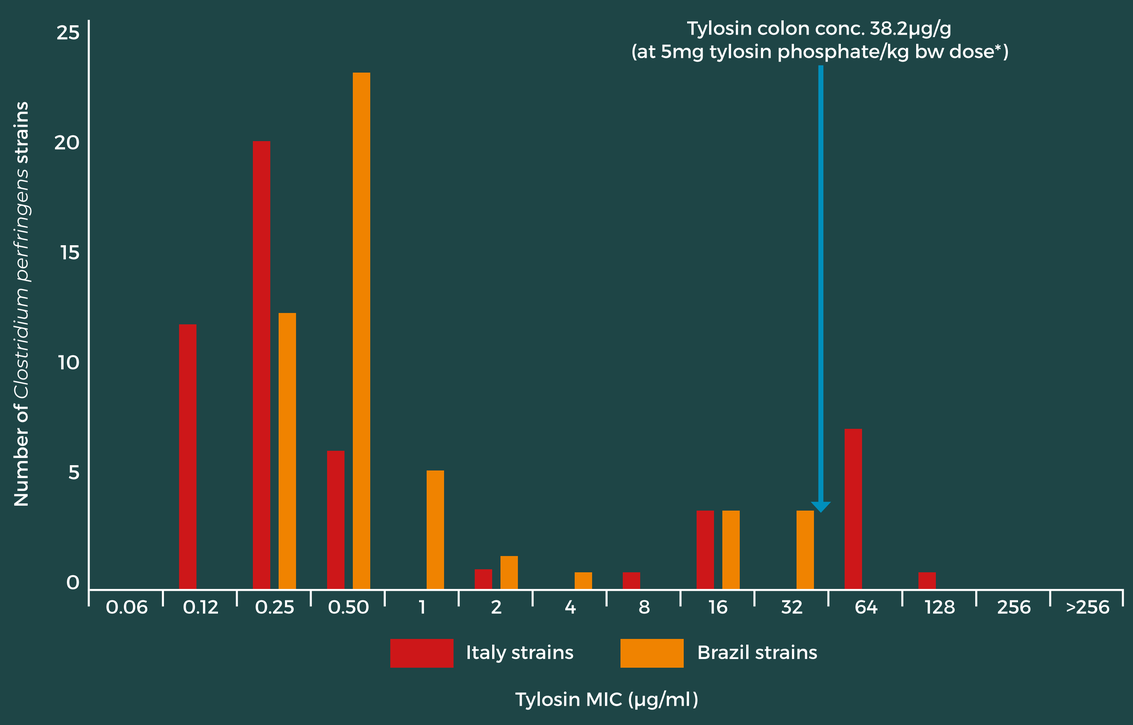
The pharmacokinetics (PK) of tylosin phosphate (Pharmasin®/ Tylovet® - Huvepharma®) colon content concentration (CCC) based on feed medication was related to tylosin MICs against *Clostridium perfringens* (CP) Type A strains (pharmacodynamics – PD).

Materials and Methods

The tylosin CCC was determined in a PK study with eleven pigs (bodyweight 20-25kg) which were medicated at a dose of 10mg/kg bw.[1] Medicated feed was offered ad libitum (5 consecutive days).

On day 5 of the PK study pigs were euthanized at 5 different time points. Tylosin PK parameters ($AUC_{0\text{-}12h}$ µg.h/g; T_{max} h; C_{max} µg/g; AUC µg.h/g/hour) were determined. AUC per hour (AUC µg.h/g/hour) was calculated to determine the tylosin CCC at registered enteric infection treatment dose (5mg/kg =100ppm) and at 10mg/kg (200ppm).

Tylosin MIC data were generated based on susceptibility testing of *Clostridium perfringens* toxinotype A strains in studies from Italy and Brazil.[2,3] 51 CP Italian and 50 CP Brazil strains were MIC tested (MIC dilutions: 0.06 - 512µg/ml). The MIC_{50}, MIC_{90} and MIC ranges were determined.



*Pharmasin®/Tylovet® registered treatment dose enteric diseases: 5mg tylosin phosphate/kg bw

Figure 1. Tylosin PK/PD relationships for *Clostridium perfringens* strains from Italy and Brazil

Results

The tylosin CCC $AUC_{0\text{-}12h}$ µg.h/g at 10mg tylosin phosphate/kg bw was recorded at 915.90 after feed medication. The CCC per hour was estimated (E) at 38.2µg/g at treatment (5mg tylosin/kg bw) and 76.3µg/g at double treatment dose. In the Italian MIC study tylosin MIC_{90} values of 64µg/ml and MIC range of 0.125-128µg/ml were measured. A tylosin MIC_{90} value of 16µg/ml and MIC range of 0.25-32µg/ml were determined for the Brazil CP strains. PK/PD relationships show that tylosin CCC´s are high and exceed the MIC values of all Brazil and 85% of the tested Italian CP strains.

Table 1. Tylosin pharmacokinetics - estimated tylosin colon content concentrations following administration at 2 different dose levels via feed

Parameter unit	Colon contents (µg.h/g)	Colon contents (average conc µg.h/g/hour) : tylosin dosage 10mg/kg bw	Colon contents (average conc µg.h/g/hour) : tylosin dosage 5mg/kg bw
$AUC_{0\text{-}12h}$ µg.h/g	915.90	E 76.3	E 38.2

Table 2. MIC ranges, MIC_{50} and MIC_{90} (µg/ml) of tylosin for *Clostridium perfringens* strains from Italy and Brazil

Publication / report	Region	N strains	MIC range	MIC_{50}	MIC_{90}
Agnoletti, F. 2021	Italy	51	0.125-128	0.25	64
Salvarani, F.M. et al. 2012	Brazil	50	0.25-32	0.5	16

Conclusion

In the case of *Clostridium perfringens* infection, an excellent therapeutic and metaphylactic effect of oral treatment with Pharmasin®/ Tylovet® premix (tylosin phosphate) can be expected based on available PK/PD data.

References

[1] Karanikolova M. *et al.* (2010). PK and PK/PD of Pharmasin® 250mg/g Premix (tylosin phosphate) following multiple oral administration in pigs. Proceedings 21st IPVS Congress, Vancouver, Canada, p.990.

[2] Agnoletti, F. (2021). Drug susceptibility of *Clostridium perfringens* field strains isolated from swine. Istituto Zooprofilattico Sperimentale delle Venezie, final report.

[3] Salvarani, F.M. *et al.* (2012). Antimicrobial susceptibility of *Clostridium perfringens* isolated from piglets with and without diarrhoea in Brazil. Brazilian Journal of Microbiology, 1030-1033.