



Pharmacokinetics of Tiamutin® administered via injection or orally

“Take home” messages

- Pharmacokinetics may be defined as the mathematical description of concentration changes of medicines within the body.
- Knowledge of these processes can enable rational dosing regimens to be established.
- Studies by McKellar and others (2004) and Anderson and others (1994) have established the lung concentrations achieved with Tiamutin® administered by injection, feed and water.
- In vitro sensitivity data on several bacterial pathogens which infect the lung, namely: *Actinobacillus pleuropneumoniae* (APP), *Streptococcus suis* (SS) and *Haemophilus parasuis* (HP) have recently been published by Fodor, L. and others (2004) and Aarestrup, F. and others (2004).
- Comparison of the in vitro sensitivity data for these organisms and the lung tissue concentrations achieved with Tiamutin® indicate that:
 - a) **APP infections can be expected to respond to Tiamutin®** injections at 15 mg thf/kg bwt for 2 to 3 days and to Tiamutin® treatments in water at 120 ppm - 180 ppm thf for 5 days.
 - b) **SS infections should be inhibited by Tiamutin®** injectable at 15 mg thf/kg bwt in feed at 110 ppm thf and in water at 60 ppm - 120 ppm thf.
 - c) **HP infections should respond to Tiamutin®** injectable at 15 mg thf/kg bwt administered for several days and in water at 120 ppm - 180 ppm thf for several days.

However in feed medication with Tiamutin® alone, at either 110 ppm or 220 ppm, is unlikely to be effective.

tiamutin
the original – tried, tested, trusted

DEVELOPED EXCLUSIVELY FOR ANIMAL HEALTH • NOT USED IN HUMAN MEDICINE



Pharmacokinetics may be defined as the mathematical description of concentration changes of medicines within the body. The duration and persistence of medicines and their metabolites in the body are studied. As a result mathematical models and concepts to describe absorption, distribution, biotransformation and excretion are developed. Knowledge of these patterns and processes for a particular medicine enables rational dosage regimes to be established.

a) Tiamutin® Injectable

Pharmacokinetic studies in the pig of the injectable formulation have been reported by McKellar and others in 2004 and by Anderson and others in 1994. McKellar and others determined the plasma and target tissue distribution of Tiamutin® Injectable following a single i/m injection equivalent to 15 mg tiamulin hydrogen fumarate per kg bodyweight.

Blood, lung tissue, colon wall and colon contents were collected and all samples stored at -20°C until analysis. The following parameters were determined:

- C max - mean maximum plasma concentration
- T max - time of C max
- AUC - area under plasma concentration time curve
- AUMC - area under moment curve
- MRT - mean residence time (See Table 1)

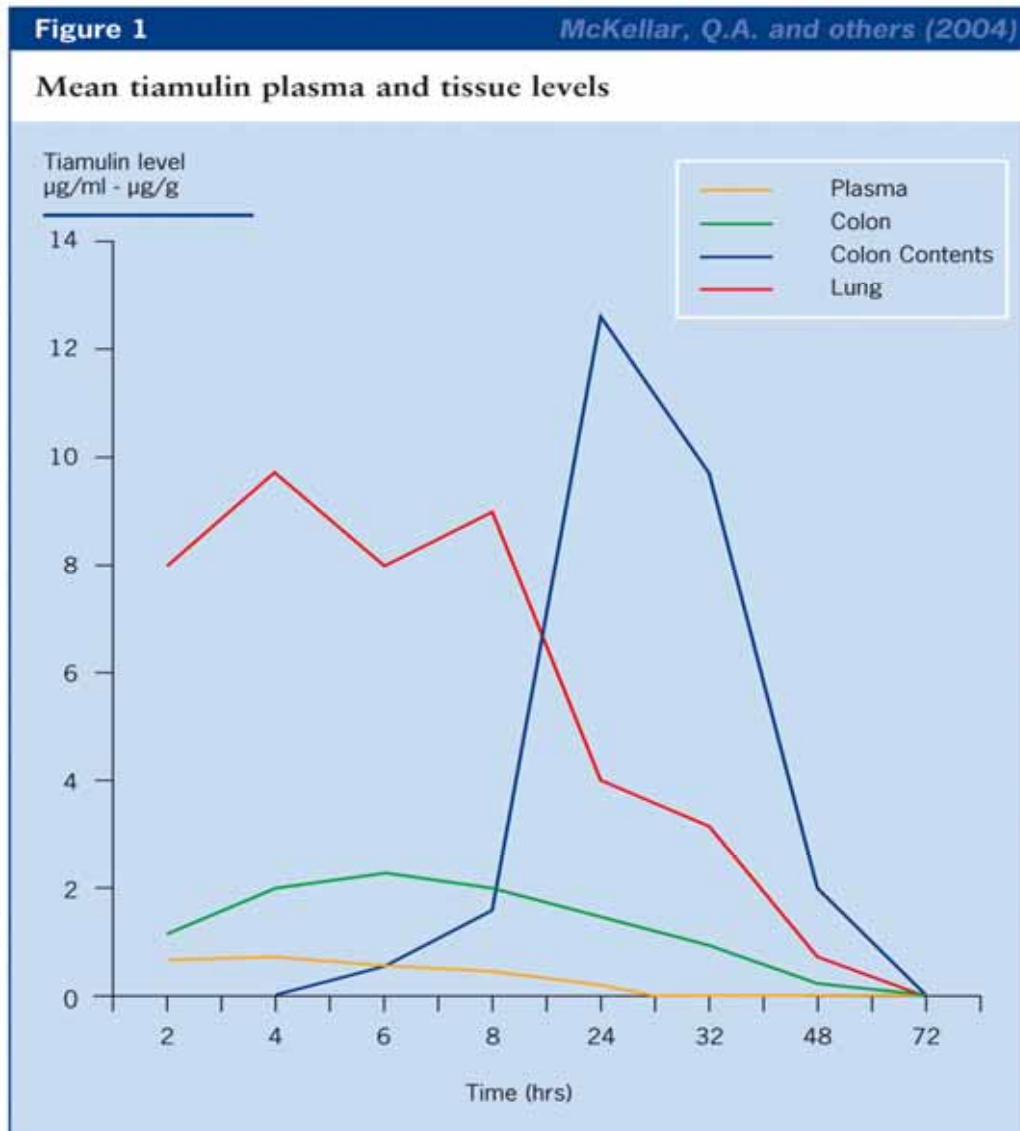
Table 1: Pharmacokinetics of tiamulin in tissues calculated from mean concentrations from each time of kill following single i/m injection of tiamulin (McKellar and others 2004)

	Plasma	Colon Wall	Colon Contents	Lung
AUC (µg h/ml)	12.82	64.51	314.23	231.52
AUMC (µg h ² /ml)	252.02	1252.78	9013.0	3868.1
MRT (h)	19.66	19.42	28.68	16.71
C max (µg/ml)	0.61	2.27	12.75	9.60
T max (h)	4.00	6.00	24.00	4.00

The C max and AUC values were very much higher for colon wall, colon contents and lung, than for plasma.



The mean tiamulin plasma and tissue levels are depicted in Figure 1 below.



The concentrations of tiamulin in the lung tissues were much higher than in plasma. The ratio of mean lung/plasma concentration were between 15:1 and 19:1 from 2 to 4 hours post-injection and even larger at 24 hrs and 32 hrs post-injection.

Mean lung concentrations were quite constant at approximately 8.0µg/g between 2 and 8 hours post-injection and were still in excess of 3.0µg/g at 32 hours post-injection.

Anderson and others (1994) administered intramuscular (i/m) doses of tiamulin base 11mg/kg and 22mg/kg bodyweight (equivalent to 13.6 and 27.2mg thf/kg bodyweight respectively) once daily for four consecutive days to groups of 5 pigs.



On the last day of medication the pigs were killed and the tissues harvested for microbiological assay. The results are shown below. (See Table 2)

Table 2: Pharmacokinetics of Tiamutin® following parenteral application

Tiamulin activity (µg/g)				
Parenteral dosage rate (thf) equivalent to	Lung	Tonsil	Colon mucosa	Colon contents
13.6 mg/kg	26.9	3.23	2.58	3.09
27.2 mg/kg	71.0	8.44	8.99	24.9

A further series of trials conducted in the USA were carried out by Anderson, M.D. and others to determine the concentration of tiamulin in certain key target tissues of the pig (e.g. lung, tonsil, colon mucosa and colon content) following oral dosage (premix and water).

b) Tiamutin® Premix

Groups of five pigs received feed containing tiamulin hydrogen fumarate at inclusion levels of 110 ppm and 220 ppm for 14 consecutive days. On the last day of medication the pigs were killed and lung, tonsil, colonic mucosa and colon contents were collected and assayed for tiamulin activity by a biological method. The actual drug dose obtained by feed consumption was calculated from the average daily intake of medicated feed. The results are depicted in the table below. (See Table 3)

Table 3: Pharmacokinetics of Tiamutin® following in feed application

		Tiamulin activity (µg/g)			
Feed inclusion level	Calculated daily dosage (thf) in mg/kg	Lung	Tonsil	Colon mucosa	Colon content
110 ppm	6.6	1.46	a	a	2.84
220 ppm	13.2	1.99	a	1.57	8.05

a = < limit of sensitivity of assay

c) Tiamutin® Water formulation

A group of five pigs received drinking water medicated with tiamulin hydrogen fumarate at levels of 60 ppm, 120 ppm and 180 ppm for five consecutive days.

On the last day of medication the pigs were killed and the tissues harvested for microbiological assay. The results of the assays are shown below. (See Table 4)

Table 4: Pharmacokinetics of Tiamutin® following water application

		Tiamulin activity (µg/g)			
Water inclusion level	Calculated daily dosage (thf) in mg/kg	Lung	Tonsil	Colon mucosa	Colon contents
60 ppm	6.2	1.11	a	a	2.16
120 ppm	13.2	4.26	a	1.56	5.59
180 ppm	20.9	8.5	2.5	3.39	18.58

a = < limit of sensitivity of assay

d) Relationship between MICs and lung levels achieved with Tiamutin®

MIC data for *Actinobacillus pleuropneumoniae* (APP) (2-4 mcg/ml, Fodor, L. and others, 2004), *Streptococcus suis* (SS) (0.015 – 0.5 mcg/ml, Fodor, L. and others, 2004) and *Haemophilus parasuis* (HP) (1-8 mcg/ml, Aarestrup, F. and others, 2004) have recently been published.

The relationship between the MIC's and the lung levels achieved with Tiamutin administered by injection, feed and water is illustrated in Table 5.

Table 5

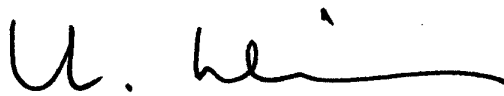
Formulation	Dose of thf provided	Tiamulin lung level (mcg/g)	Organism	MIC range (mcg/ml)
Injectable (McKellar and others)	15 mg thf/kg bwt 1 x daily	approx 8 (2-8 hrs post injection)	APP SS HP	2-4 0.015-0.5 1-8
Injectable (Anderson and others)	13.6 mg thf/kg bwt 1 x daily for 4 days	26.9 (on 4th day)		
Oral – feed (Anderson and others)	110 ppm 14 days appr. 6.6 mg thf/kg bwt/day	1.46 (on 14th day)		
	220ppm 14 days appr. 13.2 mg thf/kg bwt/day	1.99 (on 14th day)		
Oral – water (Anderson and others)	60 ppm 5 days appr. 6.2 mg thf/kg bwt./day	1.11 (on 5th day)		
	120 ppm 5 days appr. 13.2 mg thf/kg bwt/day	4.26 (on 5th day)		
	180 ppm 5 days appr. 20.9 mg thf/kg bwt./day	8.5 (on 5th day)		

e) Implications

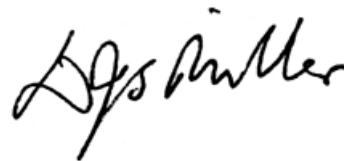
Comparing the MIC's noted above with the concentrations of tiamulin achieved in the lung:

- APP infections can usually be expected to respond to injections of Tiamutin at 15 mg thf/kg or above for 2 to 3 consecutive days and to treatments in water at 120 ppm - 180 ppm for 5 days.
- SS infections should be inhibited by injectable at 15 mg/kg bwt, in feed at 110 ppm and in water at 60 ppm - 120 ppm.
- HP infections should respond to injectable at 15 mg/kg bwt administered for several days and in water at 120 ppm - 180 ppm for several days.

However in feed application of Tiamutin alone, at either 110 ppm or 220 ppm, is unlikely to be effective.



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Further information on the Tiamutin® (tiamulin) range of products is available from the Pig Products Manager at Novartis Animal Health operations in over 50 countries worldwide.

References:

1. Aarestrup, F.M., Seyforth, A.M. and Angen, O. (2004). Antimicrobial susceptibility of *Haemophilus parasuis* and *Histophilus somni* from pigs and cattle in Denmark. *Veterinary Microbiology*. 101, p. 143-146.
2. Anderson, M.D. and others. (1994). Tiamulin activity in certain swine tissues following oral and intramuscular administration. Proc. Amer. Ass. Swine Pract (AASP). Ann. Mtg., Chicago, Illinois, USA. p 115-117.
3. Fodor, L. Stipkovits, L. and Klein, U. (2004). Sensitivity testing for respiratory pathogens of swine to antimicrobials. Proc. 18th IPVS Congress, Hamburg, Germany Vol. 2. p. 563.
4. McKellar, Q.A., Escala, J. and Szancer, J. (2004). Plasma and tissue kinetic study of tiamulin (Tiamutin®) in pigs. Proc. 18th IPVS Congress, Hamburg, Germany. Vol. 2. p. 622.