

## Use of “Tiamutin<sup>®</sup>” vs *Streptococcus suis* (Ss) infections

### “Take home” messages

- *Streptococcus suis* (Ss) is currently a key organism complicating PRDC infections (see Attachment).
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- Tiamutin is highly active in vitro vs *S. suis* – MIC range 0.015 - 2.0mcg/ml.
- Tiamutin is active intracellularly within phagocytes and produces intracellular concentrations higher than the extracellular concentration.
- Tiamutin concentrates in lung tissue when administered either orally in water/feed or by injection.
- When administered orally in drinking water at 180ppm for 5 days, tiamulin h.f. stopped deaths and increased weight gains and food consumption in Ss infected pigs, compared to infected, non-medicated controls.
- Tiamutin injectable at a dose of 15mg thf/kg bwt for 3 consecutive days is a treatment of choice. Prompt recognition of the early clinical signs and provision of early treatment will help maximize pig survival.
- Addition of an injectable anti-inflammatory corticosteroid, e.g. dexamethasone, may be beneficial in the treatment of Ss meningitis in pigs.

***In the treatment of mixed infections of PRRS virus plus Ss, Tiamutin injectable is a choice formulation.***



*Streptococcus suis* (*Ss*) is now a well-recognized pathogen of young and growing pigs and is associated with respiratory tract infections as well as meningitis, arthritis and cardiac disorders.

Tiamulin is an antibiotic which has an important potential use against *Ss* as has been shown in laboratory and experimental infection studies.

## a) In vitro studies

### 1) Sensitivity studies

Studies reported in 1988, 1996, 1999 and 2004 carried out in Holland, UK, Italy, Hungary and USA have established that *Ss* is highly susceptible to tiamulin (See Table 1 below, which shows a MIC range in 4 studies 0.015-2.0mcg/ml).

*Table 1: Results of Tiamulin MIC (mcg/ml) determinations carried out on Streptococcus suis type-2 isolates.*

	No. of strains examined	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
Pijpers, A. and others (1988/9)	20	0.25 – 2.0	1.0	2.0
Barigazzi, G. and others (1996)	611	≤0.03 – 2.0	1.0	1.0
Aitken, I.A. and others (1999)	10	1.0 – 2.0	2.0	2.0
Fodor, L. and others (2004)	10	0.015 – 0.50	0.125	0.25
Jablonski, E.A and others (2004)	5126	91.9% sensitive		

The two most comprehensive studies were conducted by Barigazzi and others (1996) in Italy and Jablonski and others (2004) in the USA. In the Italian study 611 strains of *Ss* were used and capsular type-2 represented 55.3% of all *Ss* typed in Italy at the time of the study. In the US study the results on 5126 strains represented submissions to diagnostic laboratories in three centres for the four years 1998 - 2001. All the co-operating laboratories used standardized common protocols.

Their findings were presented as % of isolates found to be sensitive to specific antibiotics. In addition antibiotic performance against particular pathogens, e.g. *Ss*, was ranked on a scale of 1 - 10, 10 being the optimum rank.

The following facts are worthy of note:

- For tiamulin 91.9% of *Ss* strains were "susceptible", whilst for tilmicosin of 3,406 strains tested, only 22.1% were "susceptible".
- The comparative rankings given to tiamulin, tilmicosin, lincomycin, tylosin, amoxicillin, trimethoprim/sulfa, ceftiofur and penicillin were as follows:

<u>Antibiotic</u>	<u>Rank vs. <i>Ss</i> (Scale 1-10)</u>
Tiamulin	9
Tilmicosin	0
Lincomycin	0
Tylosin	0
Amoxicillin	10
Trimethoprim/sulfa	10
Ceftiofur	10
Penicillin	8

Clearly on the basis of this independent US study tilmicosin, lincomycin and tylosin possess a major weakness in relation to in vitro activity vs. *Ss* in comparison with tiamulin. On the other hand tiamulin was ranked in the top four recommended agents, against *Streptococcus suis*.

## II) Intracellular activity and distribution to lungs

According to Gottschalk, M. and others writing in 1995, "antibiotics that can reach a high concentration inside phagocytes might be useful in treating *S. suis* meningitis".

Tiamulin concentrates within phagocytes, as has been reported by Nielsen and Szancer (2003). It penetrates into such cells and produces intracellular concentrations several times higher than the extracellular concentration. In regard to distribution, tiamulin is widely distributed in the body following oral and parenteral administration.

High tiamulin levels in the lungs, for example, can be achieved following such administration, which can be summarized as follows:

<u>Thf dosage level</u>	<u>Tiamulin lung tissue concentration (mcg/g)</u>
<b>Water</b>	
60 ppm	1.11
120ppm	4.26
180ppm	8.5
<b>Injection</b>	
13.6mg/kg bw	26.9

The tiamulin concentrations achieved in the lung are all (except for the 60ppm use level in water) comfortably in excess of the range of MICs of *S. suis* for tiamulin of 0.015 - 2.0mcg/ml.

## b) Experimental infection study

An experiment to confirm the activity of tiamulin hydrogen fumarate in vivo against an experimentally induced infection with *Streptococcus suis* (*Ss*) type 2 was reported by Chengappa, M. and others at the Annual Meeting of the American Association of Swine Practitioners, 5-7th March 1989. A more detailed report appeared in *JAVMA*, vol. 197, No. 11, 1st Dec 1990.

Eighteen x 4 week old pigs were purchased from a herd with no known history of *Ss* type 2 problems. All the experimental pigs had been clinically healthy since birth and were placed randomly in 3 groups A, B and C. Groups A and B (6 animals per group) were infected via a nebulizer with a log phase aerosol culture of *Ss* type 2 containing  $1.4 \times 10^{10}$  c.f.u. of *Ss*. Following challenge the pigs in Group B received 180ppm tiamulin hydrogen fumarate in their drinking water for 5 consecutive days. Group C pigs (n=6) were uninfected and unmedicated controls.

The parameters evaluated were:

- daily weight gain
- feed and water consumption
- feed efficiency
- rectal temperature
- daily clinical signs score
- clinical pathology (white cell count, fibrinogen, cortisol) at 0, 7 and 14 days
- macroscopic and microscopic lesion scores.
- bacteriological culture results.

The results obtained are illustrated in Table 2 following.



Table 2: Results from an experimental infection study

	Treatment Groups		
	A	B	C
<b>14 day data</b>			
Weight gain (kg/d/pig)	0.18±0.04	0.4±0.05	0.28±0.04
Feed consumption (kg/d/pig)	0.40±0.1	0.8±0.01	0.52±0.2
Water consumption (l/day/pig)	2.44±0.7	3.4±0.1	2.46±0.3
Feed efficacy	2.2±0.2	2.0±0.3	1.9±0.2
<b>Rectal temperatures (°C)</b>			
Day 0	38.5±0.2	39.1±0.1	39.5±0.1
Days 1-7	39.8±0.3	39.5±0.1	39.3±0.1
Days 1-14	39.0±0.2	39.5±0.1	39.3±0.2
<b>Clinical sign score/day/pig</b>			
Days 1-7	2.6±1.1	0.5±0.8	0.0±0.0
Days 1-14	1.8±1.9	0.2±0.6	0.0±0.0
<b>Total WBC count (x10<sup>3</sup> cells/mcl)</b>			
Day 0	12.7±4.6	12.6±3.2	11.3±2.2
Days 1-7	23.1±5.0	14.4±4.1	12.8±3.2
Days 1-14	20.8±7.3	13.8±3.8	13.2±2.8
<b>Fibrinogen (g/l)</b>			
Days 0	25±0.8	2.8±0.8	2.0±0.0
Days 1-7	6.3±3.3	3.5±3.3	2.4±0.9
Days 1-14	6.8±0.5	2.8±1.6	2.0±0.7
<b>Cortisol (mcg/dl)</b>			
Day 0	2.6±0.9	5.4±0.7	5.0±1.2
Days 1-7	5.4±1.0	5.1±1.2	5.7±1.7
Days 1-14	5.3±1.9	6.2±0.6	6.0±1.0
<b>Macroscopic lesion scores/pig</b>	1.8±1.8	0.2±0.4	0.0±0.0
<b>Microscopic lesion scores/pig</b>	2.3±1.5	0.5±0.8	0.0±0.0
<b>No. of pigs (out of 6) culture positive</b>			
<i>S. suis</i>	2	1	0
<i>B. bronchiseptica</i>	4	4	3
<i>M. hyorhinis</i>	6	6	6
<i>M. hyopneumoniae</i>	3	3	2
<i>H. parasuis</i>	0	0	2
<b>% recovery of <i>S. suis</i> from blood samples</b>	50%	17%	-
<b>Mortalities</b>	1/6	0/6	0/6

During the 14 day trial, pigs in Group B (medicated with tiamulin) gained weight faster than those in Group A ( $p = 0.02$ ). Pigs in Group B also consumed significantly more feed than pigs in Groups A and C ( $p = 0.009$ ).

Pigs in Group A (infected, non-medicated) had:

- significantly higher rectal temperatures for up to 5 days ( $p = 0.005$ )
- higher clinical signs scores ( $p = 0.0008$ )
- higher cortisol levels on days 7 and 14 ( $p = 0.005$ )
- higher macroscopic lesion scores ( $p = 0.03$ )
- higher microscopic lesion scores ( $p = 0.01$ )

than those in Group B.

Gross and microscopic lesions induced by *Ss* consisted of:

- meningitis
- pneumonia
- pleurisy
- pericarditis
- peritonitis
- synovitis

of varying severity and in various combinations in pigs of Groups A and B.

One pig died on day 5 in Group A with severe meningitis and arthritis. There were no mortalities in the tiamulin medicated group. *Ss* type-2 was recovered from blood in 50% of Group A but from only 17% of Group B.

The data from this investigation indicate that thf at 180ppm for 5 consecutive days in drinking water administered to young pigs with a pure *Ss* infection:

- increased weight gain
- increased feed consumption
- stopped mortalities

compared to infected, non-medicated controls.

The authors concluded that the data indicated that tiamulin (at 180ppm/thf in water for 5 consecutive days) significantly reduced the effects of *Ss* type-2 infection.

### c) Practical treatment of *Ss* infections

*Ss* infections in pigs are of 2 main types, namely:

- *Ss* as a primary pathogen usually in pigs less than 16 weeks old and affected with:
  - meningitis
  - septicaemia
  - arthritis.
- *Ss* as an opportunistic invader of the respiratory tract in co-infections with immunosuppressive viruses such as PRRS virus.

Prompt recognition of the early clinical signs of meningitis, septicaemia and arthritis followed by immediate INJECTABLE ANTIBIOTIC treatment is the most used method to maximize pig survival.

As noted in section II above, there is a clear rationale for the use of Tiamutin vs. *Ss* infections. The dose for injectable should be 15mg thf/kg bw i/m once daily for 3 consecutive days.

In human medicine it has been reported that in children affected with meningitis, fragmentation of *Streptococcus pneumoniae* elicited a severe intracranial inflammatory response which resulted in death, despite successful antibacterial action against the organism. Child mortality in this condition dropped from 30% to less than 5% when anti-inflammatory agents were added to the antibacterial treatment protocol.

In pigs Clark, L.K. (1995) in the USA reported excellent results in pigs affected with postweaning meningitis associated with *Ss* when piglets in the early stages of disease were injected simultaneously with both an antibiotic and a corticosteroid (dexamethasone).

However it should be remembered that treatment outcomes for *Ss* infection are often variable and it is not uncommon for pigs to become re-infected with *Ss* following treatment which is initially successful. Antimicrobial treatments may decrease clinical signs but do not usually eliminate the tonsillar carrier state.

#### d) Mixed PRRS virus/*Ss* infection (septicaemia/meningitis)

Halbur, P. and others (2000) reported an experiment attempting to control PRRS virus/*Ss* co-infections in piglets. A PRRS virus/*Ss* model infection utilizing 'high health' status pigs, which were weaned at 10 - 11 days of age and then acclimated in a research facility for 1 - 3 weeks was used.

PRRS virus was inoculated intranasally on day 0 and followed 7 days later by *Ss* inoculation. Co-infection without treatment typically results in 60% - 80% mortality in this model.

The following intervention strategies were investigated in the model.

- Antimicrobials:
  - penicillin injectable for 3 consecutive days p.i.
  - ceftiofur (2 groups) injectable for 3 consecutive days p.i.
  - ampicillin injectable for 3 consecutive days p.i.
  - tiamulin drinking water for 3 consecutive days p.i
- Two different modified live PRRS virus vaccines
- An autogenous killed *Ss* bacterin
- A live *Ss* vaccine

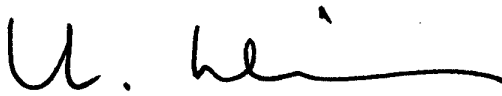
The *Ss* challenge was susceptible in vitro to all the antibiotics tested. All the antimicrobial treatments, including tiamulin h.f. in the drinking water at a dose of 23.1mg thf/kg bwt for 3 consecutive days, appeared to improve the health of the pigs during treatment. However recurrence of disease occurred shortly after cessation of treatment in the groups medicated with penicillin injection, ampicillin injection or oral tiamulin.

In this study the only treatments which significantly ( $P < 0.05$ ) reduced the mortality rate were the two injectable ceftiofur treatments and the experimental live autogenous *Ss* vaccine.

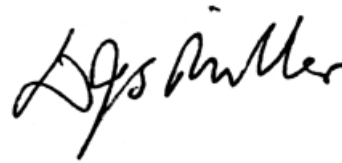
It is worthy of note that Tiamutin injectable was not included in this investigation and therefore the results achieved by ceftiofur injectable cannot be compared with those achieved by Tiamutin administered in drinking water. This would not be comparing "like" with "like".

Based on results with this model to date the authors suggested that when co-infection of PRRS virus and *Ss* occurs on a unit it is more effective to focus on treating the *Ss* infection rather than vaccinating against PRRS virus.

Tiamutin injectable at 15mg thf/kg bwt i/m for 3 consecutive days is an antibiotic, which should, in many circumstances, prove to be suitable for this purpose. However co-infection with viruses such as PRRS, which seriously degrade immunoprotection mechanisms, provides a major challenge for any antibacterial antibiotic.



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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.**

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