

PK/PD INTEGRATION OF TIAMULIN (DENAGARD®) BY INJECTION AGAINST MYCOPLASMAL JOINT INFECTIONS

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Introduction

Much of the early dose-titration work to develop effective dose rates of tiamulin injection (Denagard® – Novartis AH Inc.) for the treatment of mycoplasmal arthritis caused by *M. hyosynoviae* (MHS) was carried out before the pharmacokinetics (PK) of tiamulin in plasma or joint fluid was integrated with the pharmacodynamics (PD) or minimum inhibitory concentration (MIC) and the mycoplasma involved (Burch and Goodwin, 1984). Recent work has been reported with *M. hyorhinis* (MHR) (Talummuk et al, 2010). The purpose of this study was to review, retrospectively, the current PK/PD information and integration of tiamulin injection for these joint diseases.

Materials and method

Pharmacodynamics: Tiamulin's activity against a variety of swine pathogenic mycoplasma (Hannan et al, 1997) is summarised in Table 1.

Table 1. Susceptibility of various mycoplasma strains to tiamulin (µg/ml)

Species	No isolates	MIC 50	MIC 90	MIC range
MHS	18	0.005	0.025	0.0025-0.1
MHR	20	0.1	0.25	0.025-0.5

Goodwin (1985) showed that the minimum bactericidal concentration (MBC) was approximately 2 times the MIC for MHS and 1 times for MHR.

Pharmacokinetics: Tiamulin is considered primarily a bacteriostatic antibiotic and is co-dependent on time and concentration to exert its mycoplasmacidal effect. Therefore the area under the curve over 24h (AUC 24h) is the most suitable PK parameter to determine the potential anti-mycoplasmal effect. McKellar et al (1993 & 2004) demonstrated that the AUC 24h for tiamulin in plasma was 8.79µg.h/ml following an injection at 15mg/kg bodyweight. Combined data from McKellar et al (1993) and Skov & Nielsen (1988) showed that there was an average joint fluid concentration at 40% of the plasma concentration (range 28-59%) giving an AUC 24h of 3.52µg.h/ml (see Figure 1).

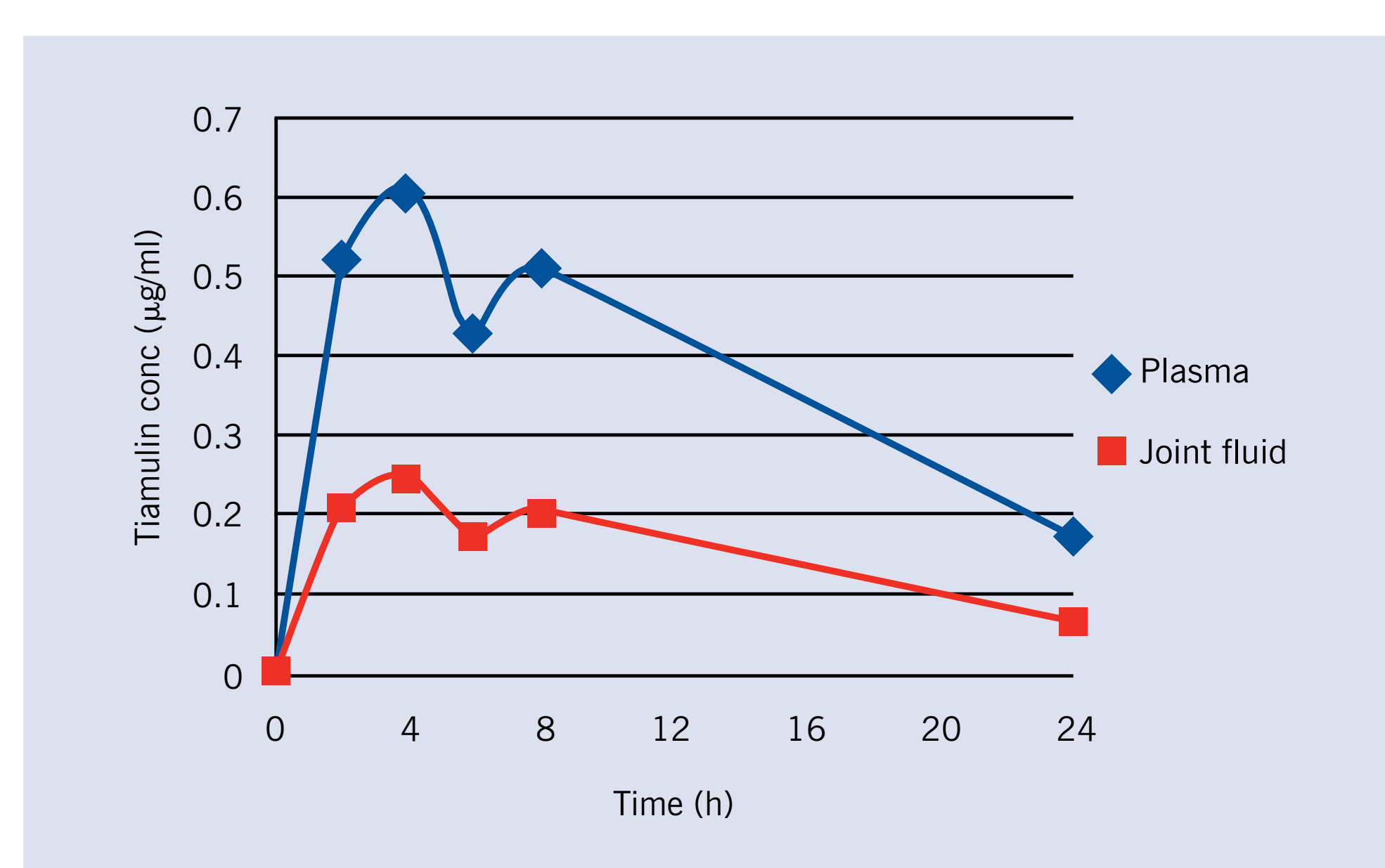


Figure 1. Comparison of plasma and joint fluid concentration following tiamulin injection at 15mg/kg bwt (based on McKellar et al, 2004)

Results and discussion

The results are summarised in Table 2.

Table 2. PK/PD integration for tiamulin using AUC24h / MBC (= MIC x MBC/MIC ratio)

Species	AUC 24h	MBC 50	MBC 90	AUC/ MBC 50	AUC/ MBC 90
MHS	3.52*	0.01	0.05	352	70
MHR	3.52*	0.1	0.25	35	14

* = AUC 24h joint fluid

Using the ≥ 100 AUC/MIC (= MBC) ratio for bactericidal antimicrobials (Toutain, 2003) and ≥ 24 AUC/MIC ratio for bacteriostatic inhibitory antibiotics, tiamulin injection would appear to exert primarily an inhibitory effect at a dose of 15mg/kg bwt against MHR at both the MBC 50 and the MBC 90, but a strong mycoplasmacidal effect against MHS's MBC 50 and a likely mycoplasmacidal effect at its MBC 90. This was confirmed clinically by Burch & Goodwin (1984) markedly reducing lameness caused by MHS in young gilts (see Figure 2). Talummuk et al (2010) demonstrated marked joint swelling reduction in nursery pigs affected by MHR polyarthritis, following treatment with Denagard Injection (see Figure 3).

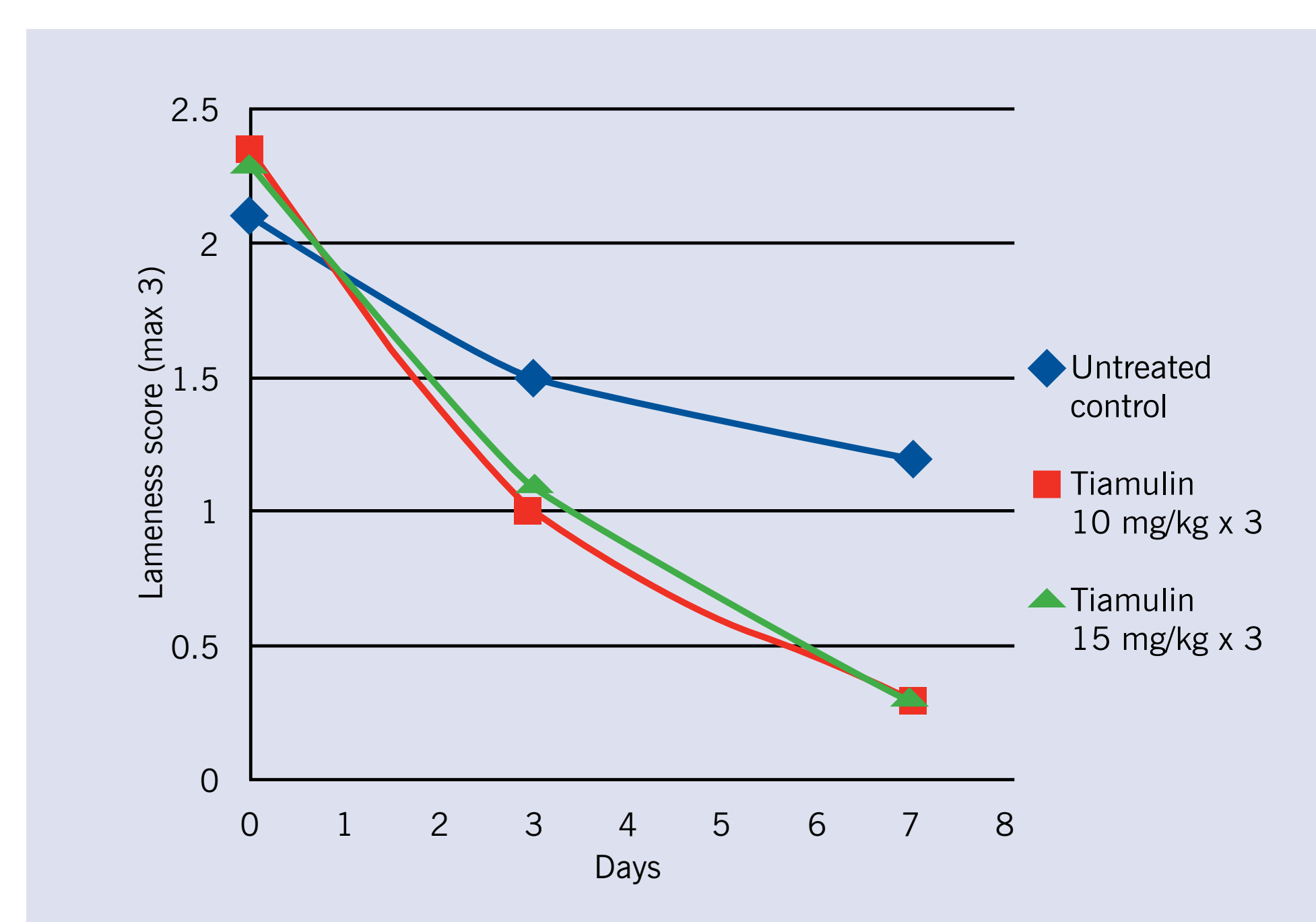


Figure 2. Treatment of mycoplasmal arthritis caused by *M. hyosynoviae* with tiamulin at 15mg/kg bwt for 3 days (Burch & Goodwin, 1984)

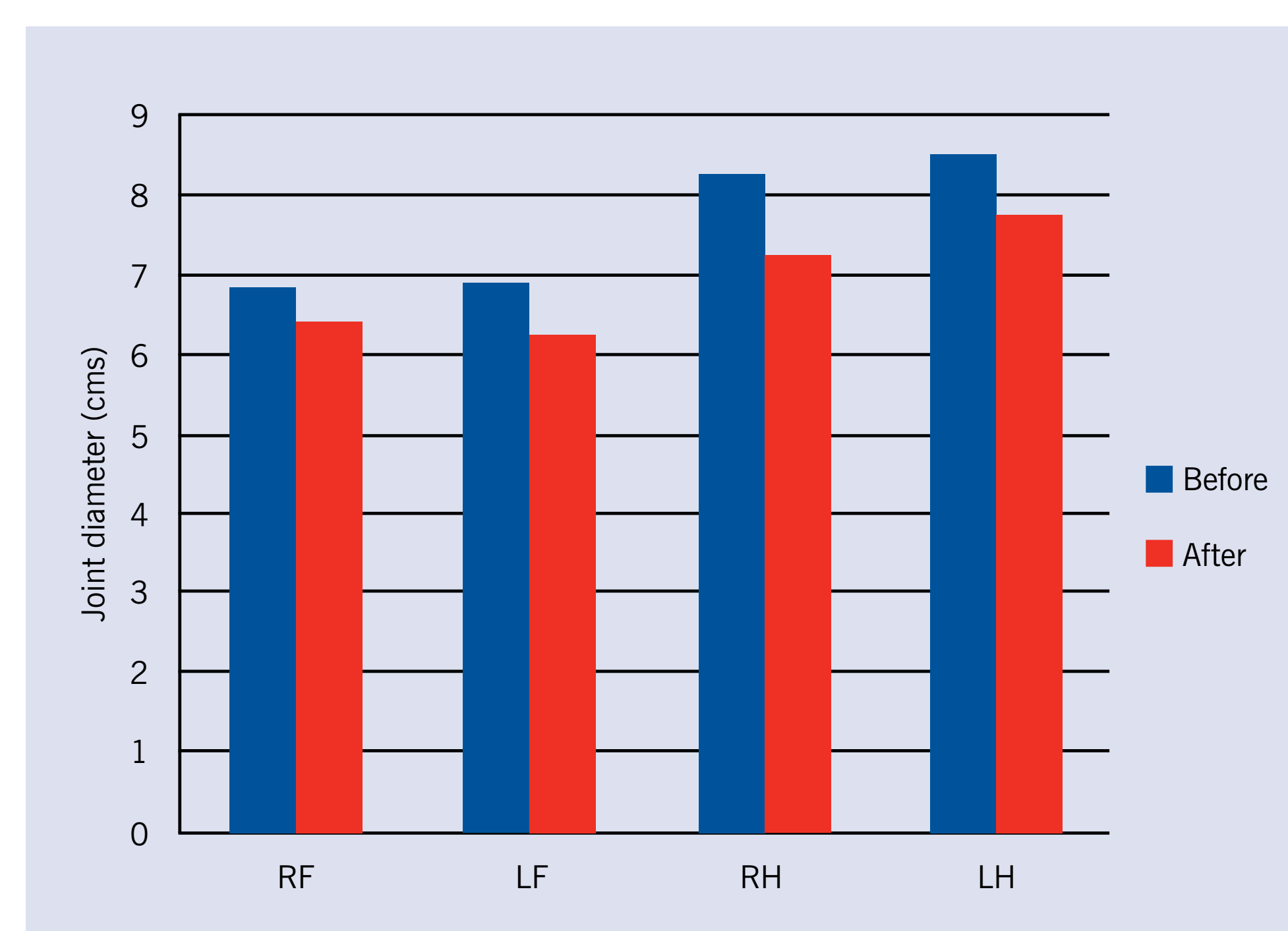


Figure 3. Treatment of *M. hyorhinis* arthritis, reduction in joint size following tiamulin injection at 15mg/kg for 3 days (Talummuk et al, 2010)



Photo 1. Mycoplasmal arthritis in a replacement gilt

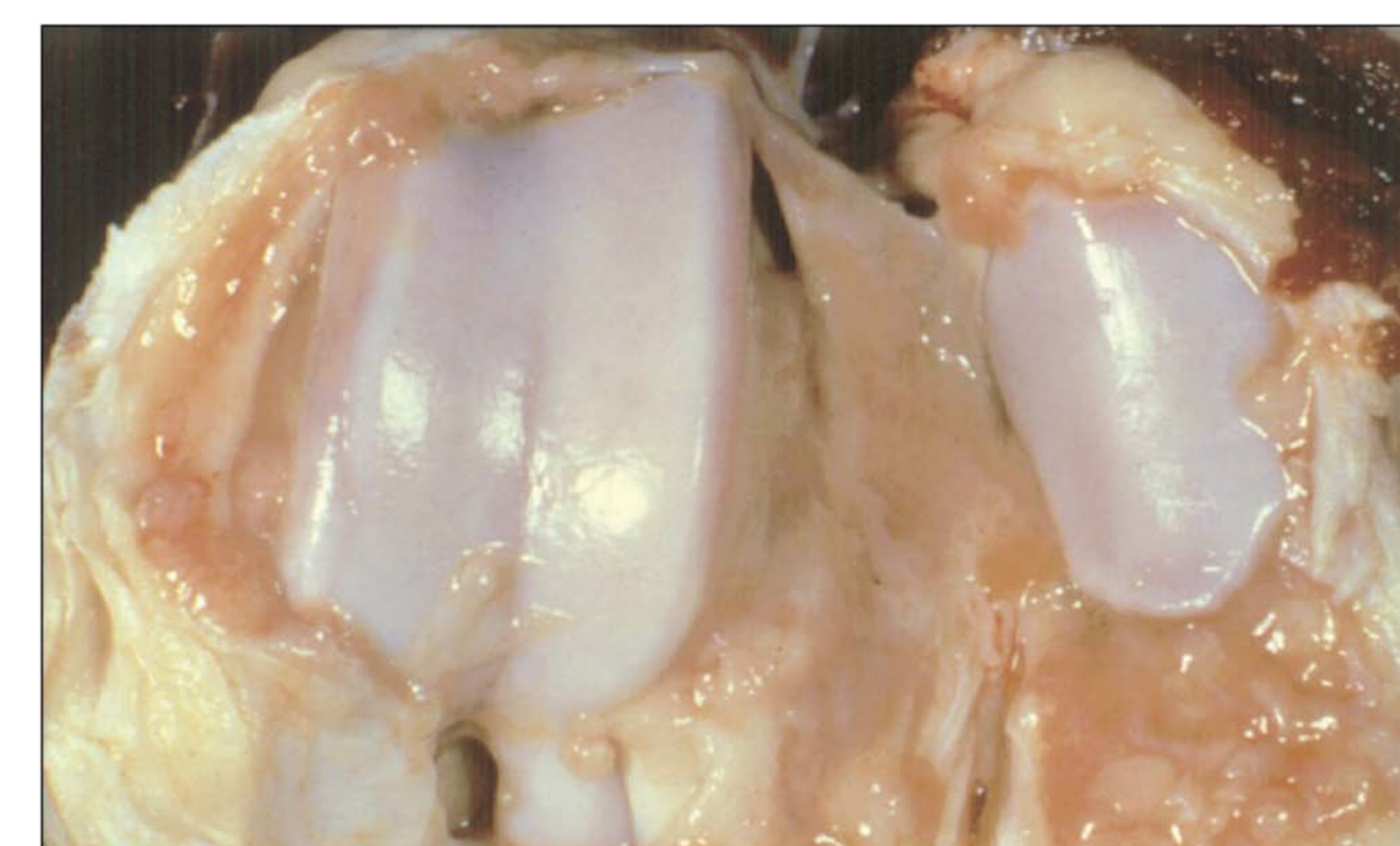


Photo 2. Mycoplasmal arthritis caused by *M. hyosynoviae*

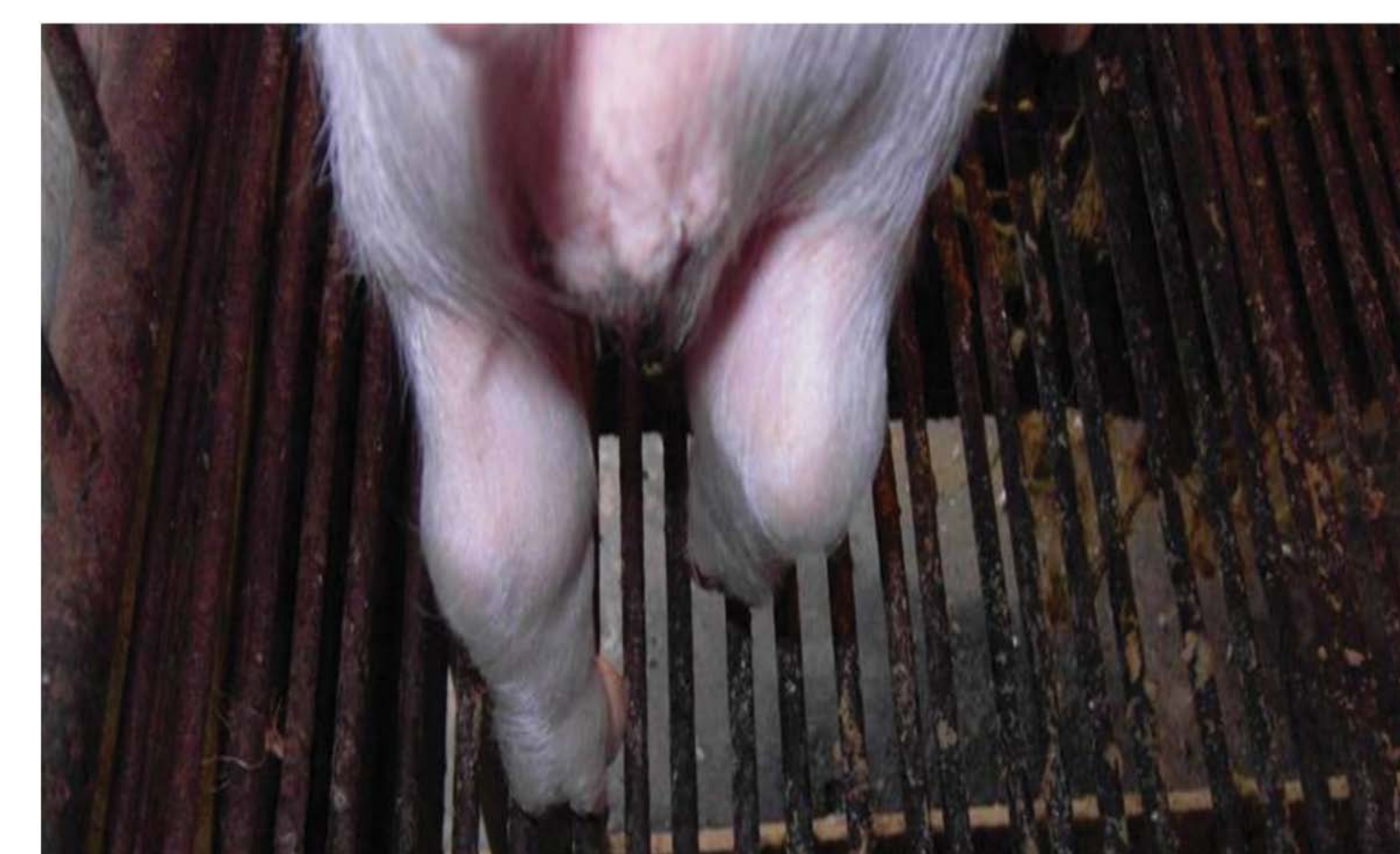


Photo 3. Mycoplasmal arthritis in a young pig caused by *M. hyorhinis*

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