Comparative activity and resistance development of tiamulin and other antimicrobials against *Avian mycoplasma*

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Introduction

Mycoplasma infection continues to be an important cause of loss in poultry production. Kleven (1990) described the losses due to *Mycoplasma gallisepticum* (MG). These were a reduction in egg production of 10-20%, an increase in embryo mortality and chick mortality of 5-10% and a reduction in weight gain and feed conversion efficiency of 10-20%. In spite of the availability of vaccines, antimicrobial use continues to be the most economic method (Stipkovits et al, 1993) of controlling these infections, where the diseases are still endemic.

As a result, resistance has developed to a number of antimicrobials and the purpose of this paper is to review the activity of tiamulin and several antimicrobials against a number of common pathogenic poultry mycoplasma, MG, *M. synoviae* (MS), *M. meleagridis* (MM) and *M. iowae* (MI) and compare their resistance development over the last 25 years.

Materials and Methods

A search of published literature was carried out and these data were combined with our own internal reports. A total of 20 references were compiled. Reports from 1975-1989 and from 1990-2000 were compared. The ranges of minimum inhibitory concentrations (MICs) of various antimicrobials against various mycoplasma species were entered into a database. The maximum and minimum data for each time period were compared for tiamulin, tylosin, oxytetracycline, lincomycin and enrofloxacin.

Results

From the 20 references and reports, 13 were from before 1990 and seven from 1990 and after. There was information on 241 isolates of MG, 105 of MS, 28 of MM and 111 of MI. The comparative data for the four mycoplasma species are summarized in the tables below.

Conclusions

MG has shown no resistance development to tiamulin over the last 25 years and all 241 isolates could be considered sensitive. In contrast there is resistance development to tylosin, oxytetracycline, lincomycin and enrofloxacin and this appears to have increased in the last decade.

MS has shown no increase in resistance to tiamulin and almost all of the 105 isolates would be considered sensitive. In contrast, resistance has developed to tylosin and oxytetracycline. Levels of resistance to lincomycin remain low and all strains could be considered sensitive to enrofloxacin.

MM isolates (28) from turkeys show some resistance to tiamulin and enrofloxacin. However, tylosin, oxytetracycline and lincomycin show a marked increase in resistance development.

MI has developed almost no resistance to tiamulin and enrofloxacin. In the nineties all isolates would be considered sensitive. High levels of resistance have developed to tylosin, oxytetracycline and lincomycin.

These findings confirm those of Drews and others (1975) and Stipkovits and Burch (1993) that tiamulin is a low inducer of resistance in mycoplasma in comparison with tylosin and slower than oxytetracycline and enrofloxacin (Stipkovits and Burch, 1993) as resistance has not developed with long-term use. Furthermore, the highest MIC level of tiamulin against MG in recent years is 16 times lower than that of lincomycin and 5 times lower than enrofloxacin.

In conclusion, tiamulin is an ideal therapeutic in mycoplasma control programs in chickens and turkeys.

Table 1. ***Mycoplasma gallisepticum*, MIC ranges (μg/ml) by time period (no. of isolates)**

Antimicrobial	1975-1989 (175)	1990-2000 (66)
Tiamulin	0.0039-0.78	0.006-0.39
Tylosin	0.01-75	0.006-400
Oxytetracycline	0.12-10	0.05-200
Lincomycin	0.4-64	0.125-6.25
Enrofloxacin	0.01-0.25	0.0125-2.0

Chart 1.

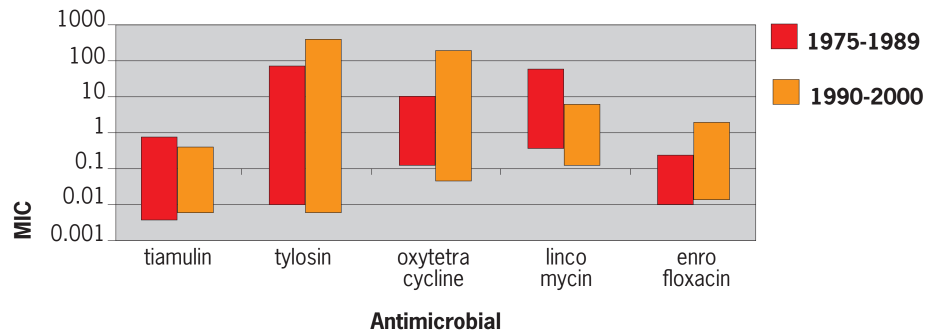


Table 2. ***Mycoplasma synoviae*, MIC ranges (μg/ml) by time period (no. of isolates)**

Antimicrobial	1975-1989 (53)	1990-2000 (52)
Tiamulin	0.031-1.0	0.006-0.5
Tylosin	0.015-75	0.006-50
Oxytetracycline	0.06-0.08	0.025-100
Lincomycin	0.31-6.0	0.05-1.56
Enrofloxacin	0.1-1.0	0.025-1.56

Chart 2.

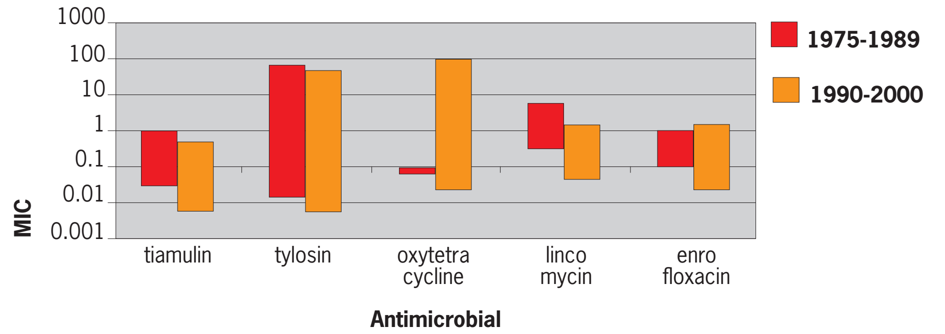


Table 3. ***Mycoplasma meleagridis*, MIC ranges (μg/ml) by time period (no. of isolates)**

Antimicrobial	1975-1989 (17)	1990-2000 (11)
Tiamulin	0.03-1.0	0.025-3.13
Tylosin	0.015-3.0	0.78-50
Oxytetracycline	0.3-5.0	0.05-25
Lincomycin	0.5-5.0	0.05-25
Enrofloxacin	0.015-1.0	0.1-3.13

Chart 3.

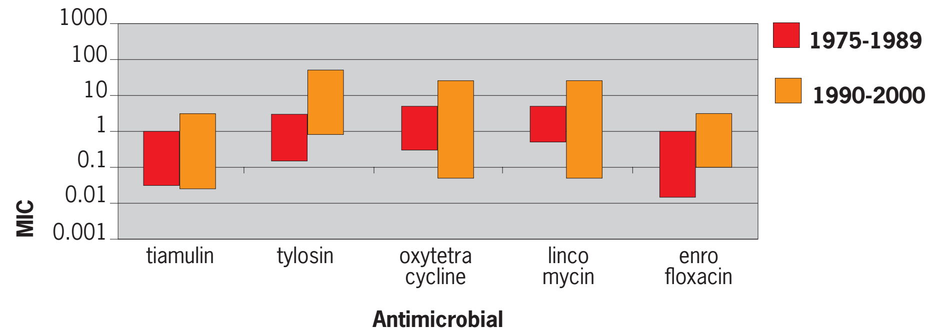
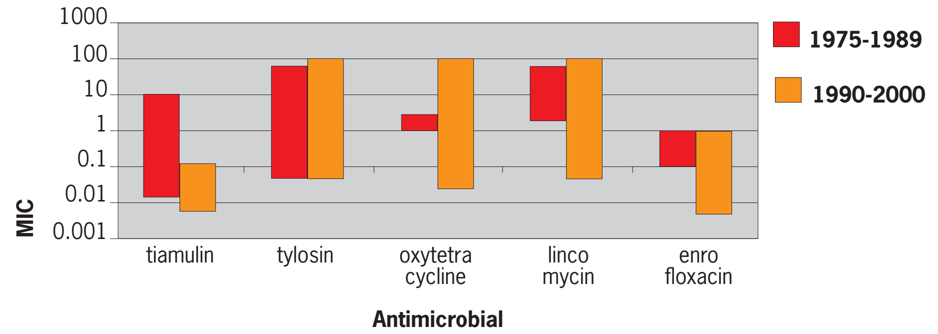


Table 4. ***Mycoplasma iowae*, MIC ranges (μg/ml) by time period (no. of isolates)**

Antimicrobial	1975-1989 (25)	1990-2000 (86)
Tiamulin	0.015-10	0.006-0.125
Tylosin	0.05-64	0.05-100
Oxytetracycline	1-3	0.025-100
Lincomycin	3-64	0.05-100
Enrofloxacin	0.1-1.0	0.005-1.0

Chart 4.



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Comparison of minimal inhibitory concentrations (MIC) against chicken mycoplasma of Tiamulin and other antimicrobials and their concentrations in the blood

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Introduction

The use of antimicrobials remains the most common means of controlling infections caused by *Mycoplasma gallisepticum* (MG) and *M. synoviae* (MS). Antimicrobial resistance has been a reported concern in many countries and a comparative overview has been recently described by Valks and Burch (ref.1). An important factor in the successful control of these infections is the correct selection and use of the antimicrobial to achieve an effective concentration in the blood of a bird so that the organism can be destroyed. Age of bird, environmental temperature, concentration of a product, and palatability are some of the variable factors that can have an effect on the water intake and dosage rate achieved. A product's pharmacokinetic characteristics of absorption, distribution, metabolism and excretion then determines the concentrations reached in the blood.

It was the purpose of this paper to compare the blood levels achieved in chickens by various antimicrobials with the reported MICs for MG and MS.

Materials and Methods

A comparative database of MIC ranges for tiamulin and various other antimicrobials against MG (241 isolates) and MS (105 isolates) had been set up (Valks and Burch, ref. 1). The literature was also searched for information on pharmacokinetic data of various antimycoplasmal products used in chickens. Some data were derived from gavage studies in which, the maximum concentration (C max) and concentration at 12 hours (C 12hrs) were determined. In other studies a steady state or average level was recorded after prolonged administration in the drinking water.

Results

The comparative MIC ranges against MG and MS are recorded in Table 1.

The comparative pharmacokinetic data for various antimicrobials are summarized in Table 2.

The comparison of the highest C max of the various antimicrobials with the MIC ranges against MG and MS are summarized in Table 3.

Conclusions

The C max varied between trials, therefore the highest reported C max for each antimicrobial was taken to make a fair comparison for each product.

Tiamulin, doxycycline and danofloxacin had MIC ranges for both MG and MS well below the C max. Tylosin, the tetracyclines and flumequine all had MIC concentrations above the C max showing some strains would be resistant to treatment. The MIC ranges for spectinomycin were completely above the C max making its efficacy very suspect. Enrofloxacin had some MICs just above the C max suggesting that there is borderline resistance and some strains may not be completely controlled.

From these results, tiamulin, doxycycline and danofloxacin would be considered very active against almost all the isolates of both MG and MS and should prove very effective. Spectinomycin is likely to be ineffective and the remaining antibiotics would have an intermediate efficacy depending on the sensitivity of the individual mycoplasma isolate.

Table 1. **Comparable MIC range (µg/ml) against MG and MS**

Antibiotic	*M. gallisepticum* (241)	*M. synoviae* (105)
Tiamulin	0.0039-0.78	0.006-1.0
Tylosin	0.006-400	0.006-75
Tetracycline	0.03-0.25	0.015-5.0
Oxytetracycline	0.05-200	0.025-100
Chlortetracycline	0.05-1.56	0.05-12.5
Doxycycline	0.006-0.2	0.0125-0.78
Spectinomycin	0.39-10	0.39-6.25
Enrofloxacin	0.01-2.0	0.025-1.56
Danofloxacin	0.01-0.78	0.1-0.5
Flumequine	2.5-10	5.0-50

Chart 1. **Comparison of MICs of MG and MS with Cmax of various antibiotics**

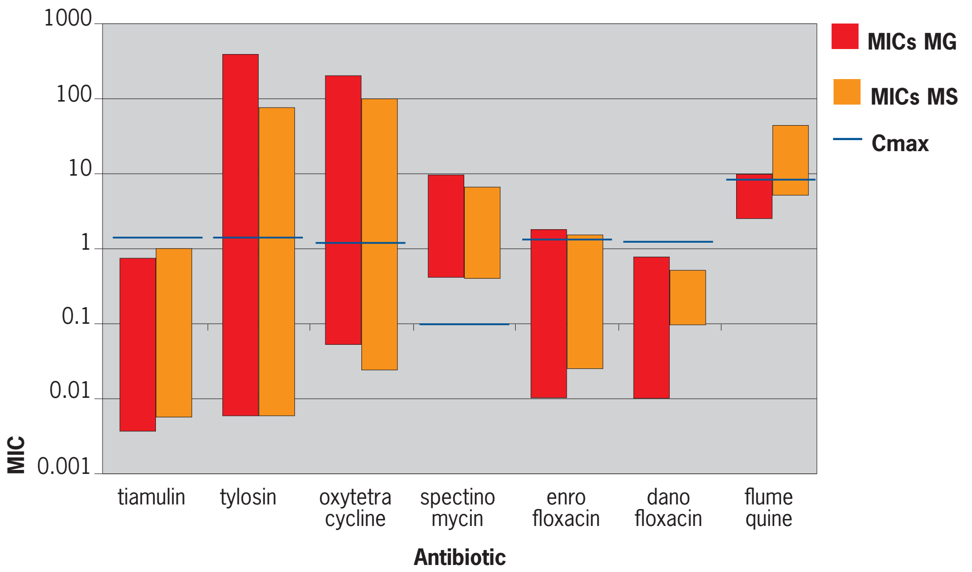

Table 2. **Comparative pharmacokinetic data for various antimicrobials in chickens**

Reference	Antimicrobial	Dose Rate (mg/kg)	Conc. Water (ppm)	C max (µg/ml)	C 12hrs (µg/ml)	Steady state (µg/ml
2	Tiamulin	25		1.7	0.17	
3		50		3.56	0.59	
			125	0.65		0.38
			250	1.4		0.78
4	Tylosin	50		4.2	0.25	
3			500	0.2		0.12
5	Tetracycline		533	0.76		0.45
6	Oxytetracycline	25		0.4	0.1	
		50		0.7	0.14	
		100		2.0	1.4	
6	Chlortetracycline	25		0.2	0.04	
		50		0.7	0.14	
		100		2.0	0.2	
		25		0.35	0.15	
7	CTC/Citric acid	25		1.48	0.15	
8	Chlortetracycline	20		0.22		
9		16	200			0.2
		32	400			0.35
		64	800			0.55
10	Doxycycline	20		54.58	7.0	
8		15		8.48		
11		11-15	100	2.2		1.9-2.2
12	Spectinomycin	33		0.08		<0.05
13	Enrofloxacin	10		1.88	0.25	
14		10	60-65			0.84
13	Danofloxacin	5		0.47	0.08	
15		5		1.85		
16		5	50			0.2
17	Flumequine	9.2				0.9
18		12		5.0	2.0	2.4
		18		9.2	1.8	

Table 3. **Comparison of C max and steady state levels (µg/ml) with MIC ranges (µg/ml) of various antibiotics against MG and MS**

Antibiotic	MG	MS	C max	Steady state
Tiamulin	0.0039-0.78	0.006-1.0	3.56	0.78
Tylosin	0.006-400	0.006-75	4.2	0.12
Tetracycline	0.03-0.25	0.015-5.0	0.76	0.45
Oxytetracycline	0.05-200	0.025-100	2.0	-
Chlortetracycline	0.05-1.56	0.05-12.5	2.0	0.55
Doxycycline	0.006-0.2	0.0125-0.78	54.58	2.1
Spectinomycin	0.39-10	0.39-6.25	0.08	<0.05
Enrofloxacin	0.01-2.0	0.025-1.56	1.88	0.84
Danofloxacin	0.01-0.78	0.1-0.5	1.85	0.2
Flumequine	2.5-10	5.0-50	9.2	2.4

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