Review

# The activity and compatibility of the antibiotic tiamulin with other drugs in poultry medicine—A review

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**ABSTRACT** Tiamulin hydrogen fumarate is a semisynthetic derivative of the diterpene antibiotic pleuromutilin used in poultry medicine to treat mainly *Mycoplasma*- and *Brachyspira*-related diseases. Its use over 30 yr has not generally increased the development of resistance to these pathogens but occasionally resistant isolates are encountered. Tiamulin administered at therapeutic levels is relatively quickly absorbed, metabolized in the liver, and eliminated from the body of the bird after a withdrawal period of 72 h, and as a result, meat products can be safely consumed. A zero withdrawal period for eggs has been granted in several European Union states. When administered with different drugs, tiamulin has been shown to have an enhanced activity with the tetracyclines. There is a strong interaction, even death, with the ionophore anticoccidials monensin, narasin, and salinomycin when tiamulin is used at therapeutic levels, but this is dose-related and low doses do not interact. It is thought to be caused by the preferential metabolism of tiamulin in the liver resulting in a build up of the ionophore leading to clinical signs of overdosage. Tiamulin shows a milder interaction, such as temporary growth depression, with maduramicin and semduramicin but is compatible with lasalocid. Although tiamulin shows small benefits in improving performance in healthy animals, its main production benefit is in the face of infection, as a true therapeutic antibiotic.

**Key words:** compatibility, poultry, medicine, tiamulin

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## INTRODUCTION

Tiamulin hydrogen fumarate (14-deoxy-14 [(2-diethylaminoethyl)-mercapto-acetoxy] mutilin hydrogen fumarate) (Denagard, Novartis Animal Health Inc.) is a semisynthetic derivative of the diterpene antibiotic pleuromutilin (Egger and Reinshagen, 1976; Figure 1) and is effectively used in the treatment of airsacculitis, which is primarily caused by *Mycoplasma* spp. Infected animals become more susceptible to different viral infections such as infectious bronchitis and Newcastle disease as well as bacterial pathogens, such as *Escherichia coli* (*coli* septicemia). This will lead to reduced growth, impaired feed conversion efficiency, and an increased rate of morbidity and mortality.

### Commercial Availability of Tiamulin

Tiamulin is available as a crystalline powder with white to yellowish color. It is commercially available in soluble formulations with 45% tiamulin hydrogen fumarate in a lactose carrier, as a 12.5% solution for inclusion in drinking water, and as a medicated feed premix, commonly 2, 10, and 80% strength, and is available in most countries of the world.

### In Vitro Susceptibility of Mycoplasma Species Against Tiamulin

One of the predominant indications for the use of tiamulin is to treat mycoplasma infections in poultry. Valks and Burch (2002) compared the minimum inhibitory concentration (MIC) values of poultry *Mycoplasma* strains *Mycoplasma gallisepticum*, *Mycoplasma synoviae*, *Mycoplasma meleagridis*, and *Mycoplasma iowae* reported between 1975 and 1989 (Table 1) and 1990 and 2000 (Table 2). The results indicated that the MIC to those species had not changed significantly over 25 yr since the introduction of the product and they remained highly susceptible to tiamulin in comparison with other antimicrobial drugs.

Recent MIC data from Europe (Pridmore, 2008) on 32 isolates of *M. gallisepticum* and 21 isolates of *M. synoviae* showed that tiamulin was generally still high-


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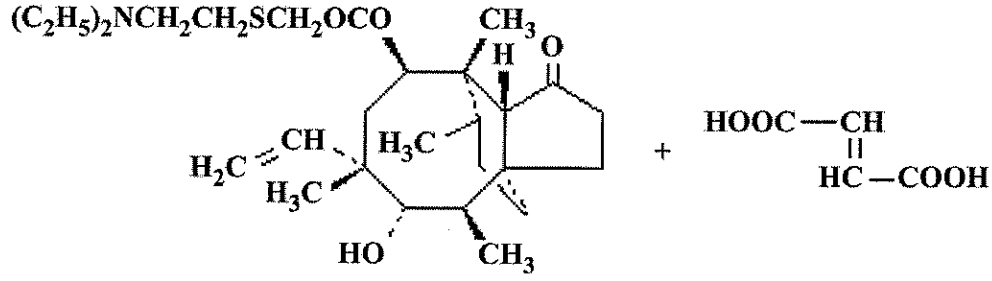


**Figure 1.** Tiamulin hydrogen fumarate.

ly active, except there were several resistant isolates of *M. gallisepticum* found in Holland only, which were tiamulin-resistant but were also co-resistant to tylosin and lincomycin (Tables 3 and 4). Lincomycin MIC were substantially higher. *Mycoplasma synoviae* isolates were generally susceptible to tiamulin, valnemulin, and tylosin but less so to lincomycin.

Tiamulin has also been shown to be highly active against *Ornithobacterium rhinotracheale* (Devriese et al., 2001) with an MIC range of ≤0.012 to 0.25 μg/mL. It has also been shown to be highly active against *Brachyspira pilosicoli* and also *Brachyspira intermedia*, which cause avian intestinal spirochaetosis mainly in layers and breeders, with MIC ranges of <0.1 to 1.0 and <0.1 to 4.0 μg/mL, respectively (Hampson et al., 2006).

In summary, tiamulin is highly active in vitro against *Mycoplasma* strains (*M. gallisepticum*, *M. synoviae*, *M. meleagridis*, and *M. iowae*), Spirochaetes (*Brachyspira hyodysenteriae*, *Brachyspira innocens*, *B. pilosicoli*, *B. intermedia*), gram-positive bacteria (staphylococci, streptococci, Clostridia, *Arcanobacterium* spp), but less active against gram-negative bacteria (*Pasteurella*, *Klebsiella*, *Haemophilus*, *Fusobacterium*, *Campylobacter*, *Bacteroides* spp.) (Werner et al., 1978; Messier et al., 1990).

## Mode of Action of Tiamulin

Poulsen et al. (2001) reported that tiamulin binds with the rRNA in the peptidyl transferase slot on the ribosome, in which it prevents the correct positioning of the CCA ends of tRNA for peptide transferase and subsequent protein production.

## Microbial Resistance to Tiamulin

According to Valks and Burch (2002), *M. gallisepticum* has shown almost no resistance development to tiamulin over the last 25 yr. These findings are supported by other scientists (Drews et al., 1975; Stipkovits and Burch, 1993), who have demonstrated that tiamulin is generally a low inducer of resistance in *Mycoplasma*. Some *M. iowae* tiamulin-resistant mutants were also resistant to both macrolide antibiotics (Gautier-Bouchardon et al., 2002).

Bøsling et al. (2003) indicated that tiamulin targets the 50S subunit of the bacterial ribosome and interacts at the peptidyl transferase center, from studies with tiamulin and resistant *E. coli*. The authors concluded that the L3 mutation on the ribosome, which points into the peptidyl transferase cleft, causes tiamulin resistance by alteration of the drug-binding site.

## Tiamulin Content in Blood and Body Tissues

After oral gavage of the medicine at 25 and 50 mg/kg of BW, tiamulin rapidly reaches peak serum concentrations of 1.7 and 3.6 μg/mL, respectively, in chickens at about 2 h; the levels declined over a 12- and 24-h period depending on dose (Laber and Schütze, 1977).

Ziv (1980) worked with broiler chickens with supplemented 125 and 250 mg of tiamulin/L in the drinking water for 48 h and found that the steady state levels were 0.38 and 0.78 μg/mL, respectively, in serum. A clinical breakpoint of 1.0 μg of tiamulin/mL is commonly used for systemic and respiratory infections. Tiamulin is rapidly absorbed from the gastrointestinal tract of chicken and is primarily metabolized in the liv-

**Table 1.** Antimicrobial sensitivity ranges of various antimicrobials (μg/mL) against *Mycoplasma gallisepticum* (MG), *Mycoplasma synoviae* (MS), *Mycoplasma meleagridis* (MM), and *Mycoplasma iowae* (MI), isolated between 1975 and 1989 (Valks and Burch, 2002)

| Antimicrobial | MG (175)[1] | MS (53) | MM (17) | MI (25) |
|---|---|---|---|---|
| Tiamulin | 0.0039 to 0.78 | 0.031 to 1.0 | 0.03 to 1.0 | 0.015 to 10 |
| Tylosin | 0.01 to 75 | 0.015 to 75 | 0.015 to 3.0 | 0.05 to 64 |
| Oxytetracycline | 0.12 to 10 | 0.06 to 0.08 | 0.3 to 5.0 | 1 to 3 |
| Lincomycin | 0.4 to 64 | 0.31 to 6.0 | 0.5 to 5.0 | 3 to 64 |
| Enrofloxacin | 0.01 to 0.25 | 0.1 to 1.0 | 0.015 to 1.0 | 0.1 to 1.0 |

[1]Number of turkey and chicken isolates is in parentheses.

**Table 2.** Antimicrobial sensitivity ranges of various antimicrobials (μg/mL) against *Mycoplasma gallisepticum* (MG), *Mycoplasma synoviae* (MS), *Mycoplasma meleagridis* (MM), and *Mycoplasma iowae* (MI), isolated between 1990 and 2000 (Valks and Burch, 2002)

| Antimicrobial | MG (66)[1] | MS (52) | MM (11) | MI (86) |
|---|---|---|---|---|
| Tiamulin | 0.006 to 0.39 | 0.006 to 0.5 | 0.025 to 3.13 | 0.006 to 0.125 |
| Tylosin | 0.006 to 400 | 0.006 to 50 | 0.78 to 50 | 0.05 to 100 |
| Oxytetracycline | 0.05 to 200 | 0.025 to 100 | 0.05 to 25 | 0.025 to 100 |
| Lincomycin | 0.125 to 6.25 | 0.05 to 1.56 | 0.05 to 25 | 0.05 to 100 |
| Enrofloxacin | 0.0125 to 2.0 | 0.025 to 1.56 | 0.1 to 3.13 | 0.005 to 1.0 |

[1]Number of turkey and chicken isolates is in parentheses.

er. Donoghue (2003) indicated that after oral dosing of chickens, total $C^{14}$ radiolabeled antiobiotic residues exceeded the tolerance for the first day of withdrawal. By the second day, however, the residues in edible tissues were lower than the tolerance of the test (0.3 μg/g). Considering the above aspects, different companies recommended 2- to 7-d withdrawal after treatment via the drinking water but a zero withdrawal period for eggs.

## In Vivo Effectiveness of Tiamulin

The in vivo effectiveness of tiamulin against *Mycoplasma* strains was initially evaluated in artificial infection studies in chickens and turkeys (Laber and Schütze, 1975; Baughn et al., 1978) and confirmed in the field by Stipkovits et al. (1977). The studies recommended that the tiamulin concentration in drinking water for treatment of mycoplasmosis in chickens and turkeys was 250 and 125 mg/L for prophylaxis.

More recent studies have shown that tiamulin is highly effective in the treatment of avian intestinal spirochaetosis in breeder and layer hens at 25 mg/kg of BW per day over 5 d in artificial infection studies with *B. pilosicoli* and *B. intermedia*, respectively (Hampson et al., 2002; Stephens and Hampson, 2002). It was confirmed by Burch et al. (2006) in a field infection with *B. pilosicoli* in laying hens but at 12.5 mg/kg for 3 d.

In some cases, secondary bacterial invaders, such as *E. coli*, complicate mycoplasmosis. *Pasteurella multocida* and more recently *Ornithobacterium rhinotracheale* have been identified as major causes of respiratory problems in turkeys and broilers. A broader spectrum product such as chlortetracycline or doxycycline can be used in combination with tiamulin for mixed infections and a synergistic activity has been reported (Burch and Stipkovits, 1993) against *Mycoplasma* and some bacteria such as *P. multocida*.

## Effect of Tiamulin on the Performance of Poultry

A substantial increase in growth rate over controls in chickens infected with *M. gallisepticum* was observed when treated with tiamulin (Jordan et al., 1998). Kleven (1990) described that *M. gallisepticum* reduces egg production by 10 to 20%, increases embryo mortality and chick mortality by 5 to 10%, and reduces weight gain and feed conversion by 10 to 20%. The use of antimicrobial substances like tiamulin was considered the most economic method (Stipkovits et al., 1993) of controlling these infections, especially in broiler breeders. Horrox (1980) also indicated that treatment with tiamulin at 250 mg/L did not influence the hatchability of turkey eggs. In broilers with no clinical disease, the inclusion in feed of 30 mg/kg along with 90 mg/kg of chlortetracycline had little effect on performance in the presence of 60 mg/kg of salinomycin either when fed continuously or intermittently (Islam et al., 2007a,c,d, 2008a,b) but did improve zootechnical parameters substantially in *M. gallisepticum*-challenged birds (Stipkovits et al., 1999; Islam et al., 2007a,b). No adverse effect was detected in broilers when co-administered with semduramicin (Islam et al., 2007d) or with chlorotetracycline and salinomycin (Afrin et al., 2008).

## Interaction of Tiamulin with Other Drugs in Farm Animals

Tiamulin is compatible with tetracyclines in broilers (Burch and Stipkovits, 1994), but it was shown to be incompatible with nitrovin (Noa et al., 2000), a former growth promoter in pigs and poultry, but signs indistinguishable from a hypersensitivity reaction (uneasiness, anxiety, skin erythema, and rash on snout, vulva, and

**Table 3.** Susceptibility of 32 isolates of *Mycoplasma gallisepticum* against tiamulin, valnemulin, tylosin, and lincomycin (Pridmore, 2008)

| Antibiotic | MIC[1] 50 (μg/mL) | MIC 90 (μg/mL) | Range (μg/mL) |
|---|---|---|---|
| Tiamulin | 0.008 | 1.0 | ≤0.004 to >256 |
| Valnemulin | 0.008 | 1.0 | ≤0.004 to 64 |
| Tylosin | 0.016 | 4.0 | 0.008 to >256 |
| Lincomycin | 4.0 | 64 | 0.25 to >256 |

[1]MIC = minimum inhibitory concentration.

Table 4. Susceptibility of 21 isolates of *Mycoplasma synoviae* against tiamulin, valnemulin, tylosin, and lincomycin (Pridmore, 2008)

| Antibiotic | MIC[1] 50 (μg/mL) | MIC 90 (μg/mL) | Range (μg/mL) |
|---|---|---|---|
| Tiamulin | 0.125 | 0.25 | ≤0.004 to >0.5 |
| Valnemulin | 0.008 | 0.008 | ≤0.004 to 0.016 |
| Tylosin | 0.031 | 0.62 | 0.008 to 0.25 |
| Lincomycin | 0.5 | 2.0 | 0.125 to 4.0 |

[1]MIC = minimum inhibitory concentration.

increased body temperatures) disappeared spontaneously 4 to 5 d after ceasing medication.

Clinically important, often lethal interactions between the ionophore anticoccidials and the antibiotic tiamulin are a well-known phenomenon in chickens and turkeys and have been reported for more than 2 decades. This incompatibility is well established for monensin, salinomycin, and narasin and to a much lesser extent in severity to maduramicin (Hanrahan et al., 1981; Frigg et al., 1983; Weisman et al., 1983; Umemura et al., 1985; Van Vleet et al., 1987; Laczay et al., 1989; Mazurkiewicz et al., 1989a; Szucs et al., 2000; Croubels et al., 2001). Although the nature of this interaction remained unknown for many years, Meingassner et al. (1979) concluded from his findings that tiamulin reduced metabolic degradation and excretion of monensin in chickens and led to an overdosing effect. This conclusion is in agreement with the observation that principally the same toxic signs (loss of appetite, locomotor disturbances, ataxia, and neurotoxicity) were seen after administration of monensin alone at high levels or in combination with tiamulin at standard usage levels (Hanrahan et al., 1981; Umemura et al., 1985; Van Vleet et al., 1987; Mazurkiewicz et al., 1989a; Szucs et al., 2000).

The clinical signs (after feeding maduramicin, lasalocid, monensin, narasin, or salinomycin at use levels together with tiamulin) were associated with marked disturbances in the transport of ions (i.e., sodium, potassium, calcium, magnesium, iron, zinc, and copper) between myocytes and intercellular space (Mazurkiewicz et al., 1989b). Sakar et al. (1991a,b) demonstrated that tiamulin caused muscle damage reflected by the increasing level of related enzymes in blood serum in pigs, while administered with narasin or monensin, but withdrawal of both drugs reduced the enzymes to normal levels within a few days Histological and ultrastructural examination of muscle tissues in broilers after administration of maduramicin, lasalocid, monensin, narasin, or salinomycin at normal use levels together with tiamulin at 20 mg/kg of BW revealed myopathies and cardiomyopathies (Madej et al., 1993). The alterations originated from primary mitochondrial lesions followed by adenosine triphosphate deficiency, edema, degeneration, and necrosis of myocytes.

The interaction is dose-dependent of tiamulin and coadministered drugs like polyether antibiotics as well as ionophore coccidiostats like semduramicin, monensin, and salinomycin (Meingassner et al., 1979; Weisman et al., 1980, 1983; Stipkovits et al., 1992; Lehel and Laczay, 1995; Lehel et al., 1995). Stipkovits et al. (1992) showed in laboratory and field experiments that 20 to 30 mg of tiamulin/kg of feed and 60 mg of salinomycin/kg sustain maximum growth of broilers, which were infected with *M. gallisepticum* and are therefore compatibile at these levels. Antioxidants reduced the severity of toxic symptoms in swine and chicken (Van Vleet et al., 1987; Laczay et al., 1994; Lehel et al., 1995).

Later, further toxic interactions of other drugs with polyethers (mainly monensin) became known. Studies by Frigg et al. (1983) indicate that sulphonamides increase the toxicity of monensin. Also, the co-administration of chloramphenicol (Broz and Frigg, 1987), erythromycin, oleandomycin, and furazolidone with monensin gave similar results (Anadón and Martinez-Larrañaga, 1990; Anadón and Reeve-Johnson, 1999).

Recent data indicate that the interaction of polyethers with tiamulin and macrolide antibiotics involves their influence on the microsomal cytochrome P-450 isoenzymes, which play an important role in the oxidative and reductive metabolism of numerous endogenous and exogenous compounds. An important group of drugs forming these metabolic intermediate complexes is the macrolide antibiotics (Larrey et al., 1983; Watkins et al., 1986). Through the formation of intermediate complex, they inhibit and induce the cytochrome P-450. Certain N-demethylation and hydroxylation processes were strongly inhibited by tiamulin (Witkamp et al., 1994). The interaction with cytochrome P-450 appears to be selective on enzymes of the P-450 3A subfamily, although some interactions with P-450-1A1 may occur (Witkamp et al., 1995, 1996). Monensin itself does not exert significant effects on microsomal liver enzymes (Szucs et al., 2000). However, P-450 3A plays an important role in the oxidative metabolism of monensin (Nebbia et al., 1999). Compounds capable of binding or inhibiting these isoenzymes could therefore be expected to give rise to toxic interactions with the ionophore(s). Because the relative toxicities of the ionophores (within and across species) vary considerably (Oehme and Pickrell, 1999), the polyethers show remarkable differences concerning the severity of toxic interactions.

In 1984, it was shown that lasalocid sodium might be the only ionophore that could be exposed concomitantly with tiamulin without adverse effects (Comben, 1984). Sakar et al. (1992) demonstrated that the activity of aspartate amino transferase and creatine kinase was within the normal range in blood after the continu-

**Table 5.** Live weight, feed intake, and feed conversion efficiency during coadministration of tiamulin and semduramicin in broiler chicks (54 g at start)

| | Semduramicin (mg/kg of feed) from d 1 to 35/tiamulin (mg/L of water) from d 15 to 19 | | | |
|---|---|---|---|---|
| Item | None/None | None/250 | 25/none | 25/250 |
| No. of replicates (cages) | 10 | 10 | 10 | 10 |
| Chicks per replicate | 8 | 8 | 8 | 8 |
| Live weight (g) | | | | |
| 14 d | 547 | 545 | 542 | 540 |
| 21 d (tiamulin administration) | 1,003[a] | 996[a] | 994[a] | 936[b] |
| 28 d | 1,497[ab] | 1,520[a] | 1,527[a] | 1,458[b] |
| 35 d | 2,062 | 2,067 | 2,084 | 2,008 |
| Total feed intake (g) | 3,018[a] | 3,009[a] | 2,996[a] | 2,877[b] |
| Feed conversion efficiency (g of weight gain/kg of feed intake) | 665 | 669 | 678 | 679 |

[a,b]Different superscripts in the same row differ significantly ($P < 0.05$).

ous administration of tiamulin and lasalocid. Lodge et al. (1988) confirmed also the compatibility of lasalocid (125 mg/kg of feed) with tiamulin (125 mg/L of water) in turkeys.

A laboratory study indicated that semduramicin at 20 to 30 mg/kg (the routine use level) was well tolerated when co-administered with tiamulin (250 mg/kg of feed; Ricketts et al., 1992). This result disagreed with data reviewed by SCAN (2002) indicating that the concurrent medication of birds receiving 25 mg of semduramicin/kg of feed with tiamulin in water (250 mg/L) for 3 d resulted in a minor depression of weight gain and deterioration in feed efficiency. Other relevant data such as hematology, clinical chemistry, gross pathology, and histopathology from treated animals with this combination were not available. In their opinion, SCAN considered the time of tiamulin administration as short in comparison to recent recommendations for tiamulin treatment (up to 5 d) and therefore no proof was given for the compatibility of semduramicin and tiamulin in broilers. Recent findings (Table 5) indicated that tiamulin co-administration caused temporary depression of weight gain and feed intake without causing clinical symptoms, but generally recovered within 17 d (Schuhmacher et al., 2006, 2007; Islam et al., 2007c) and increased feed conversion efficiency numerically.

It may be concluded that the tiamulin, as an antibiotic, can be useful in poultry production for the treatment of *Mycoplasma* and *Brachyspira* spp. infections. It should not be used with the ionophore anticoccidials monensin, salinomycin, and narasin because severe interactions including death will occur. With maduramicin and semduramicin, some minor reductions in growth and feed conversion can be expected, but the birds recover within a few days. Tiamulin is compatible with lasalocid in chickens and turkeys. Its administration at lower dose rates inhibits *M. gallisepticum*, the causal agent of chronic respiratory disease, and consequently the birds may not suffer from depression of performance. This is especially important in the presence of the incompatible ionophore anticoccidials, but resistance to the pathogen may develop. Its effect in noninfected birds was insignificant on their performance, which suggests its main beneficial effect is as a therapeutic medicine.

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