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Review

TULATHROMYCIN – A SEMI-SYNTHETIC MACROLIDE ANTIBIOTIC. II. USAGE IN VETERINARY MEDICINE

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Summary

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This article presents the results of studies on the use of the new macrolide antibiotic tulathromycin in veterinary medicine. The information is presented according to the species of domestic animals, diseases, doses and shemes for therapy and metaphylaxis. The first section includes data for cattle and calves affected by respiratory diseases, caused by *M. haemolytica*, *M. bovis*, *H. somni* and *P. multocida,* and keratoconjunctivitis caused by *M. bovis*. The second one shows data for swine and pigs affected by the respiratory pathogens *A. pleuropneumoniae*, *P. multocida*, *H. parasuis*, *B. bronhiseptica* and *M. hyopneumoniae*. A third group presents information about small ruminants with manifested respiratory diseases caused by *M. haemolytica*, *P. multocida*, *Mycoplasma spp.*, *Pseudomonas spp.* and hoof diseases from *Dehelobacter nodosus*. Fourth group includes the first test results of *Rhodococcus equi, Streptococcus zooepidemicus, Theileria equi, Babesia bovis and Babesia bigemina,* causing diseases in horses. The fifth section includes reports of treated rabbits most commonly suffering from *P. multocida* respiratory infections. Finally, data from new studies on the use of tulathromycin in exotic animals and cases of some tropical diseases are listed. The provided information gives proof for the high sensitivity of the tested pathogens to tulathromycin and high clinical and economical effect that is efficient in single dose of 2.5 mg/kg. Compared to other antibacterial agents there is no resistance according to data available so far. Local accumulation and prolonged persistence of the drug in lung tissues, that result in a treatment regime with a single low-volume dose (2.5 mg/kg), are associated with positive clinical outcome in domestic animals: large ruminants, pigs, small ruminants and rabbits with respiratory diseases caused by *M. haemolytica, H. somni, P. multocida* and *M. bovis; A. pleuropneumoniae*, *B. bronchiseptica, P. multocida, H. parasuis* and *M. hyopneumoniae; S.aureus, C. pseudotuberculosis* and *Streptococcus spp.* and *P.multocida.*

Key words: animals, antibiotics, diseases, doses, effectiveness, macrolides, tulathromycin

The article is focused on application of tulathromycin in veterinary practice. In search of a new antibiotic that meets the requirement for high efficacy against bovine respiratory disease (BRD) and swine respiratory disease (SRD) with a single

treatment, scientists have found a new subclass of macrolides, previously called triamilides, with high activity against Gram-negative respiratory pathogens, desirable pharmacological characteristics, ensuring high and prolonged tissue levels in domestic animals (Letavič, 2002; Nowakowski *et al.*, 2004; Villarino *et al.*, 2013). Tulathromycin is formulated as an aqueous solution for a single parenteral injection throughout the course of treatment against respiratory bacterial pathogens in cattle, pigs and sheep at 2.5 mg/kg (Letavič, 2002).

USE IN CATTLE AND CALVES.

Tulathromycin is a new semi-synthetic, triamilide antibiotic of the macrolides group used for the treatment and metaphylactics of BRD associated with *M. haemolytica*, *M. bovis*, *H. somni* and *P. multocida* and for the treatment of infectious bovine keratoconjunctivitis caused by *Moraxella bovis.* It is administered *s.c.* at 2.5 mg/kg. As an undesirable reaction, tulathromycin can cause painful reaction, bleeding, oedema and fibrosis at the injection site (Letavič *et al.*, 2002; Evans, 2005; Godinho *et al.*, 2005a,b; USPC, 2007). BRD is the most common cause of disease and mortality in North American calf fattening farms. *M. haemolytica* is often isolated from calves with BRD and the prevalence of antibiotic resistance (AR) of this organism has increased in recent years (Crosby *et al.*, 2018).

The fattening calves from 2 commercial farms with clinical signs of BRD were divided into two groups, the first treated with tulathromycin (2.5 mg/kg, s.c.) and the second: with enrofloxacin (12.5 mg/kg, s.c.). Treatment with tulathromycin was reported to result in higher treatment success (87.9%, P=0.009 and 80%, P=0.031, for farms 1 and 2, respectively). The treatment of calves with enrofloxacin led to recovery in 70.2% and 62.5%, respectively. In addition, animals receiving tulathromycin also had a higher weight gain than those receiving enrofloxacin (Robb *et al.*, 2005).

In France, Germany, Italy and Spain, the effectiveness of tulathromycin in the treatment of BRD has been tested at commercial farms. Introduced calves with clinical signs of disease were treated with tulathromycin (n=128) or florfenicol (n=125). A comparable percentage of animals (83.3% of those receiving tulathromycin and 81.0% of those treated with florfenicol) showed lasting clinical improvement to day 14 and to the 60th day, no need from re-treatment in 63.3% of the tulathromycin group and in 58.4% of the group with florfenicol (Godinho *et al.*, 2005b).

The efficacy and safety of using tulathromycin as a single dose for the treatment of 2,000 castrated male calves with undifferentiated BRD have been evaluated in field trials conducted in 4 different US pastures. The groups were treated: with saline solution (n=160), 0.02 mL/kg s.c.; with tulathromycin (n=320), 2.5 mg/kg s.c.; with tilmicosin (n=320) at 10 mg/kg s.c. It was reported that the proportion of cured calves treated with tulathromycin (78%) and tilmicosin (65%) was significantly higher than those treated with saline (23.8%). The results of this experiment suggested that tulathromycin given as a single dose was effective for the treatment of undifferentiated BRD in calves (Kilgore *et al.*, 2005a,b).

The bacterial etiology of BRD in calves has been studied in Turkey, through nasal swabs examination. *M. haemolytica* – 27.5%, *P. multocida* – 22.5%, *K. pneumoniae* – 10%, *M. haemolytica*+ *Streptococ-*

cus spp. – 10%, *P. multocida*+*Streptococcus* spp. – 5% and *Streptococcus* spp. – 5% were isolated. The animals of group 1 received s.c. a single dose of 2.5 mg/kg tulathromycin, and of group 2 a single dose of 10 mg/kg tilmicosin. On day 5, the proportion of recovered animals was reported, which was 85% for group 1 and 80% for group 2. In conclusion, the injectable administration of tulathromycin and tilmicosin was considered to be effective in the treatment of BRD in calves (Aytekin *et al.*, 2010).

In a controlled study conducted by Bartram *et al.* (2016) the efficacy of tulathromycin and tildipirosin given by single s.c. injection at 2.5 and 4.0 mg/kg respectively was compared for treatment of experimental infection with *Mycoplasma bovis* in calves (n=238) infected by endobronchial inoculation. The infected calves were divided into three groups for treatment with tulathromycin, tildipirosin and saline. Tulathromycin-treated calves had a lower percentage of lungs with lesions (P=0.0079), lower mortality (P=0.0477), fewer days with depression (P=0.0486), and higher live weight (P=0.0112) than tildipirosin-treated calves.

In a field trial conducted in Nebraska, the comparative therapeutic efficacy of tulathromycin (s.c., 2.5 mg/kg) and florfenicol (s.c., 40 mg/kg) in grazing calves and fever of unknown origin (FUO) was tested (Schunicht *et al.*, 2007). The calves have been neither vaccinated against *M. haemolytica* and *H. somni* nor treated metaphylactically with antibiotics. The first FUO recurrences, higher mortality and mortality from BRD in the tulathromycin group were significantly lower than those in the florfenicol group. The former group showed higher carcass quality than the latter one.

Nautrup *et al.* (2013) have studied the clinical and economic results of tulathromycin used as a first-line BRD treatment agent in grazing grown calves in the United States, compared to other antibiotics. Two effects from the treatment of calves at a high risk from BRD development were established: one as means for control of compared drugs and the other as a model for tulathromycin treatment at first clinical BRD manifestations. For comparison, florfenicol and tilmicosin were used in both models, while enrofloxacin was included only in the tulathromycin treatment model. Treatment with tulathromycin was found to result in more first treatments with success and several recurrences (in chronic cases) throughout the comparison. Due to the higher efficacy, overall costs during the initial study period were always lower for the tulathromycin model. These results, and the few episodes of BRD in tulathromycin-treated calves, not only support the general prevention and management of BRD, but also reduce the need for repeated antibiotic treatments and maintain the line for the rational use of antibiotics in animal husbandry.

The clinical efficacy of tulathromycin for reducing incidence of disease and mortality from BRD has been tested in 1,239 calves reared on 4 farms under grazing conditions (Kilgore *et al.*, 2005a). Calves, 413 in a group, were treated s.c. with saline of 0.02 mL/kg, tulathromycin 2.5 mg/kg or tilmicosin 10 mg/kg before showing clinical signs of BRD. Respiratory disease mortality was the highest in saline injected calves and markedly lower in calves treated with tulathromycin or tilmicosin. Mortality from BRD was significantly ($P \leq 0.0001$) higher in tilmicosin-treated calves compared to tulathromycin-treated ones. Tulathromycin administered

to calves at high risk of developing BRD was considered significantly more effective in reducing mortality than saline and tilmicosin treated animals.

The effectiveness of tulathromycin for the protection of calves from BRD has been tested on commercial farms,. On the 14th day after treatment, significantly more calves receiving tulathromycin regained their good clinical condition (92.4%), while calves that received tilmicosin – 83.7% and saline – 63.7%. This condition persisted until day 60, at 85.4% for tulathromycin, 75.1% for tilmicosin, and 56.2% for saline (Godinho *et al.*, 2005b,c).

The therapeutic efficacy of tulathromycin in BRD in young heifers caused by *Mycoplasma bovis* infection was tested by Gudinho *et al.* (2005c). Two highly pathogenic *M. bovis* strains (MIC for tulathromycin of 1 and >64 μg/mL) and 145 heifers were used for this purpose. Four days after inoculation, heifers with signs of BRD were treated subcutaneously (s.c.) with saline or tulathromycin (2.5 mg/kg). Heifers with signs of BRD, elevated rectal temperature and pulmonary lesions were significantly fewer in the tulathromycin-treated group ($P<0.01$). This allowed the authors assuming that tulathromycin was highly effective in treating *M. bovis* induced BRD in heifers, regardless of the MIC value of the infectious strain.

In a comparative study on the efficacy of enrofloxacin and tulathromycin to control BRD in calves at risk of developing the disease, 33.7% of calves that received enrofloxacin required treatment for BRD within the first 45 days of receipt, compared to 18.3% of the calves that received tulathromycin ($P=0.040$). Calves from the two groups that required more than one treatment for BRD during the first 45 days of arrival did not differ significantly. The percentage of dead calves during the 45-day period was 12.2% for the enrofloxacin-treated and 10.1% for the tulathromycin-treated ($P=0.592$), respectively (Crosby *et al.*, 2018).

The metaphylactic effect of tulathromycin administration against BRD in fattening calves has been evaluated by changes in the parameters of ruminal fluids (Fiore *et al.*, 2016). Animals in the metaphylactic BRD treatment group were injected with tulathromycin 2.5 mg/kg, and control animals received placebo. Statistically significant differences ($P<0.05$) were found between the treated and the control groups in terms of low values of rumen pH (6.02 vs. 5.89) on the 8th day after treatment. The obtained daily weight gain increased on the average by 8.6 kg in the treated group ($P<0.05$). Changes in the pH of the rumen and the volatile fatty acid values suggested the effect of tulathromycin administration, such as BRD metaphylaxis, which was expressed by modulation of rumen fermentation, in particular on the 8th day after administration.

In one study, Amrine (2013) found that metaphylactic administration of antibiotics 10 days prior to the experimental inoculation of cows from 5 different holdings with *M. haemolytica,* demonstrated fewer lung lesions and fewer clinical signs of the disease than cows treated with tulathromycin.

USE IN SWINE AND PIGS

Tulathromycin has been tested and used for the treatment and metaphylaxis of swine respiratory disease (SRD), caused alone or as a co-infection by *A. pleuropneumoniae*, *P. multocida, H. parasuis*, *B. bronchiseptica* and *M. hyopneumoniae.* Following intramuscular injection of pigs, single cases of transient response, mani-

festedas discomfort for several minutes, may occur. In pigs over 80 kg, up to 2 mL of tulathromycin was injected at one site. After 2 days, the effect of the treatment was evaluated. If the disease continued, the antibiotic was changed (Evans, 2005).

The effectiveness of a single dose of tulathromycin given at 2.5 or 5 mg/kg and ceftiofur given at 3 mg/kg for 3 days, was evaluated in pigs with respiratory disease experimentally induced with *A. pleuropneumonia*. Up to the 10th day after infection, the following parameters were recorded: rectal temperature, clinical signs of respiratory disease, general condition of pigs and number of deaths. No animals treated with 5 mg/kg tulathromycin or 3 mg/kg ceftiofur were culled. The reported increase in pigs treated with antimicrobial agents was significantly ($P<0.05$) higher than in the saline group. A lower percentage ($P<0.05$) of total pulmonary changes and incidence of *A. pleuropneumoniae*-related respiratory disease was also reported (Hart *et al.*, 2006).

It was concluded that a single dose of tulathromycin administered i.m. to pigs may proprotect them against severe porcine pleuropneumonia and death up to the 9th day (Waag *et al.*, 2008).

The therapeutic efficacy of tulathromycin was evaluated in weaned pigs inoculated *i.n.* with *M. hyopneumooniae*. The non-infected (control) pigs remained healthy, with no lungs affected. Compared with the saline group, in the tulathromycin-treated group, the cough, lung lesions, and proportional lung weight were significantly less and the mean daily increase was significantly higher ($P<0.05$). Compared with enrofloxacin-treated patients, there was no significant difference in proportional lung weight or mean daily growth, but cough and lung lesion values were higher in the tulathromycin-treated group ($P<0.05$). In conclusion, tulathromycin was estimated to be effective in the treatment of pneumonia following experimental *M. hyopneumoniae* infection (McKelvie *et al.*, 2005).

The clinical efficacy of tulathromycin in the treatment of naturally occurring SRD was studied in five European countries. Pigs 1 to 6 months of age showing clinical signs of disease were treated i.m. with tulathromycin at 2.5 mg/kg on day 0, against tiamulin at 15 mg/kg on day 0, day 1 and day 2 (Germany, Netherlands and UK) or florfenicol at 15 mg/kg on days 0 and 2 (France). The most commonly diagnosed pathogens were *A. pleuropneumoniae*, *P. multocida* and *M. hyopneumoniae*. Mean rectal temperature and the most common clinical signs on day 2 and day 10 were significantly ($P=0.0001$) reduced in animals treated with tulathromycin, tiamulin or florfenicol compared to day 0. No significant difference ($P>0.05$) was found between treated pigs with respect to the average daily gain. It is concluded that tulathromycin can be a good protective and highly effective agent for the treatment of naturally occurring SRD (Nanjiani *et al.* 2005).

Field trials involving 720 fattening pigs were performed in four North American pig farms with manifestations of SRD in order to test the efficacy of injectable tulathromycin at a single dose of 2.5 mg/kg compared to the ceftiofur treated group, 3 mg/kg for 3 consecutive days and saline-treated control group. The proportion of deaths was significantly smaller in the groups treated with tulathromycin and ceftiofur compared to those treated with Saline. Cultures of *A. pleuropneumoniae*, *P. multocida*, *H. parasuis* and *M. hyopneumoniae* were isolated from dead pigs. Under field conditions, a single i.m. dose 2.5 mg/kg tulathromycin as solution for injec-

tion protected and was effective in treating SRD (Nutsch *et al.*, 2005).

USE IN SMALL RUMINANTS

Tulathromycin has been tested for the treatment of respiratory diseases in sheep and goats and infectious pododermatitis (foot rot) associated with the virulent *Dehelobacter nodosus*. A dose of 2.5 mg/kg, equivalent to 1 mL/40 kg body weight, was administered i.m. into the neck. The efficacy of tulathromycin in sheep with severe clinical signs or chronic foot rot is limited, so its use is appropriate only in the early stages of the disease (USPC, 2007; Washburn, *et al.*, 2009; Villarino *et al.*, 2013).

Naccari *et al.* (2015) presented the results of a study on the effectiveness of tulathromycin in the treatment of respiratory infections in sheep. Gram-negative *M. haemolytica*, *P. multocida*, *M. ovipneumoniae* and *Pseudomonas spp.* strains were isolated in bacteriological studies. A single dose of tulathromycin (2.5 mg/kg) was injected s.c. into the neck of each sheep. In treated animals, the symptoms of the disease decreased after the second day, and after 5–7 days, they disappeared completely, with a return to normal respiratory activity. In the absence of other literature data, the authors assumed that this was the first therapeutic use of tulathromycin in sheep by injection.

At the same time, Jafary *et al.* (2015) have tested the therapeutic efficacy of tulathromycin in sheep and goats in Iran affected by infectious pneumonia. Animals were injected s.c. with 2.5 mg/kg. Studies indicate that *Pasteurella spp*. was isolated from all sheep and goats before injection, whereas on day 3 it was isolated from only 2 animals ($P \leq 0.05$); *Mycoplasma spp*. was isolated from 57.9% of small ruminants and the results were identical in the second cultivation, except for one animal, and 50% and 44.4% of sheep and goats euthanised on day 9 and day 15 after tulathromycin injection showed different pulmonary lesions, adhesions, bronchopneumonia and pleuritis. Based on these studies, it was suggested that tulathromycin had no antibacterial effect on *Mycoplasma spp.*

In a study by Washburn *et al.* (2009) an acceptable clinical response of goats with abscesses of caseous lymphadenitis caused by *Corynebacterium pseudotuberculosis* treated with tulathromycin was reported.

APPLICATION IN HORSES

Pneumonia is one of the main causes of mortality in young horses. *Streptococcus equi subspecies zooepidemicus* (*S. zooepidemicus*) and *Rhodococcus equi* are two of the major causes of the disease at 1 to 6 months of age (Hoffman *et al.*, 1993; Cohen, 1994). *In vitro* studies showed low activity of tulathromycin against *R. equi* isolates which have MIC_{50} and MIC_{90} over 64 μg/mL (Carlson *et al.*, 2010). Tulathromycin administered i.m. at a dose of 2.5 mg/kg can be used for the treatment in the initial stages of bronchopneumonia, but compared to azithromycin-rifampin, the pulmonary lesions after one week of treatment were larger and therapy is longer.

In an *in vitro* study, Silva *et al.* (2018) found that tulathromycin, at relatively low concentrations, showed good characteristics as a growth inhibitor in *Babesia bovis*, *Babesia bigemina* and *Theileria equi*. Three times more tulathromycin was required to completely inhibit *B. bovis* growth with IC_{50}, which is approximately 3 times higher than IC_{50} of *B. bigemina*

and approximately 7 times higher than IC_{50} of *T. equi*. Until now, treatment of acute bovine babesiosis and equine theileriosis has been achieved through the use of chemotherapeutics to which the organisms are already resistant, leading to the need for new, safe and effective drugs (Mosqueda *et al.*, 2012; Hines *et al.* 2015). Although *in vitro* tests confirmed the efficiency of the antibiotic, it's use needs to be validated in clinical settings.

APPLICATION IN RABBITS

Pasteurella multocida is the etiologic agent of purulent rhinitis in rabbits. The *P. multocida* vaccine reduces the infection but does not provide complex protection under farm conditions. Because the immunisation is a passive, antibacterial treatment is the first choice for control of the disease. Because tulathromycin is retained in the lungs for many days after a single application, it can be used to treat respiratory diseases in rabbits. (Benchaoui *et al.*, 2004; Evans, 2005; AyseEr *et al.*, 2011; Edrees *et al.*, 2017).

It was found that treatment of male rabbits with tulathromycin led to increased levels of blood troponin I, creatine kinase-MB, and creatinine, and decreased white blood cell counts, ionised calcium, and potassium levels. The authors assumed that tulathromycin may cause cardiotoxicity, but its effect was perhaps less dangerous than that of other macrolide drugs commonly used in veterinary medicine (Ayse Er *et al.*, 2011).

In vivo treatment of experimentally infected rabbits with *P. multocida* with tulathromycin improved the clinical signs, the proportion of deaths, the number of lesions and the growth parameters in infected rabbits (Edrees *et al.*, 2017). In addition, treatment with tulathromycin improved the haematological picture and lowered levels of biochemical parameters that were significantly elevated during infection, such as liver enzymes, blood urea, creatinine, and creatine kinase, and led to increase in total protein and albumin levels. These biochemical data were supported by histopathological findings. The authors concluded that tulathromycin was an ideal and safe antibiotic for treatment of *P. multocida* infections in rabbits.

USE IN EXOTIC ANIMALS AND TROPICAL DISEASES

According to Gull *et al.* (2012) the use of broad-spectrum antibiotics in zoo animals is a good alternative in cases of enzootic diseases. In turn, tulathromycin facilitates therapy because of its broad spectrum of activity and not yet registered resistance. Compared with antibiotics such as cefovecin, ceftazidime, ceftiofur and oxytetracycline, only single, subcutaneous or intramuscular administration is required.

A pharmacokinetic study of tulathromycin by Kinney *et al.* (2014) in desert turtles (*Gopherus agassizii*), showed good results with intramuscular application at a dose of 5 mg/kg. Liquid chromatography and spectrophotometry have demonstrated a long elimination half-life ($T_{½}$el) of 77.1 h and recorded plasma concentrations up to 240 h after the administration of tulathromycin. It is accepted that the antibiotic can be successfully used as an alternative in the treatment of upper respiratory tract disease in turtles, because of its proven efficacy against *Mycoplasma* and Gram-negative bacteria.

Stegmann *et al.* (2017) used tulathromycin at a dose of 2.5 mg/kg in combination with 0.2 mg/kg flunixin meglumine after surgery in crocodiles, requiring prolonged isoflurane anaesthesia.

A study conducted by Villarino *et al.* (2015) showed good activity of tulathromycin against *Plasmodium yoelii*, which causes malaria in rats. Malaria plasmodium resistance is a problem for the World Health Organization (WHO), which impedes disease control (WHO 2011; Maxmen, 2013). With monotherapy at a dose of 25 mg/kg s.c. in the scapula area of mice infected with *P. yoelii*, parasitaemia prevention was observed, with a peak on day 17. Such studies offer new possibilities for the administration of this semisynthetic, triamilide antibiotic.

CONCLUSION

It is established that tulathromycin, administered s. c. to calves and heifers at 2.5 mg/kg, could be used for treatment and methaphylaxis of BRD, associated with *M. haemolytic*a, *M. bovis, H. somni, P. multocida, K. pneumonia* and *Streptococcus spp.* and for treatment of keratoconjunctivitis caused by *Moraxella bovis*. In compatative trials for the therapeutic efficacy of tulathromycin with enrofloxacin, florfenicol, tilmicosin and tildipirosin the application of single dose of tulathromycin has been significantly effective in BRD treatment of calves and heifers, with better clinical and economic results. Tulathromycin administered as a single dose at 2.5 or 5 mg/kg s.c. or i.m., was effective for the treatment of SRD in pigs, caused by *A. pleuropneumoniae, H. parasuis* and *M. hyopneumoniae.* In comparative trials of tulathromycin with tiamulin, florfenicol and ceftiofur, tulathromycin was more effective in protection and treatment of SRD, resulting in prolonged protection, reduction of respiratory incidents, lower mortality and higher daily weight gain. In tulathromycin-treated sheeps and goats with *M. haemolytica, P. multocida, M. ovipneumoniae* and *Pseudomonas spp.* pneumonia, the symptoms of the disease decreased after the second day and disappeared completely after 5–7 days. Tulathromycin was also an ideal and safe antibiotic for the treatment of *P. multocida* infections in rabbits. The inhibitory effects of tulathromycin against certain pathogens and parasites in horses, revealed its potential for the prevention and treatment of diseases caused by them. The use of tulathromycin in the case of enzootical infectious diseases in zoos and reserves is a good alternative to the antimicrobials used so far, in crocodiles, desert turtles, rats and mice.

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