YYU Veteriner Fakultesi Dergisi, 2010, 21 (3), 159 - 162
ISSN: 1017-8422; e-ISSN: 1308-3651

ORIGINAL ARTICLE

Effects of Tulathromycin and Tilmicosin Application in the Treatment of Bovine Respiratory Disease in Cattle

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Received: 30.07.2010 Accepted: 10.08.2010

SUMMARY

This study aims to determine bacterial etiology of the respiratory system diseases in cattle and to compare the clinical effects of tulathromycin and tilmicosin treatments. For this purpose, nasal sıvabs were taken from 40 different animals with respiratory disease, and bacterial agents were isolated from these samples. Consequently, agents and the rates of isolation were determined *Pasteurella haemolytica* 27.5%, *Pasteurella multocida* 22.5%, *Klebsiella pneumonia* 10%, *Pasteurella haemolytica+streptococcus spp.* 10%, *Pasteurella multocida+streptococcus spp.* 5% and *Streptococcus spp.* 5%. Study divided in two groups consisting of 20 animals each. One dose of 2.5 mg/kg tulathromycin was applied in group 1, and one dose of 10 mg/kg tilmicosin was applied subcutaneously in group 2. Recovery rate in five days was determined as 85% in group 1 and 80% in group 2. In conclusion, both tulathromycin and tilmicosin administration was found to be effective in the treatment of bovine respiratory disease of cattle.

Key Words *Bovine respiratory disease, Etiology,Tulathromycin, Tilmicosin, Treatment*

Sığırlarda Solunum Sistemi Hastalığının Tedavisinde Tulathromycin ve Tilmicosin'in Etkisi

ÖZET

Bu çalışmada, sığırlarda solunum sistemi hastalıklarının bakteriyel etiyolojisinin belirlenmesi ve tedavisinde tulathromycin ile tilmicosin uygulamasının klinik etkinliklerinin karşılaştırılması amaçlandı. Solunum sistemi hastalığı belirlenen toplam 40 adet hayvandan burun sıvapları alındı ve bu örneklerden bakteriyel etken izolasyonu yapıldı. Etken izolasyonu sonucu *Pasteurella haemolytica* %27.5, *Pasteurella multocida* %22.5, *Klebsiella pneumonia* %10, *Pasteurella haemolytica+streptococcus spp*. %10, *Pasteurella multocida+streptococcus spp*. %5, *Streptococcus spp*. %5 olarak izole edildi. Çalışmada solunum sistemi hastalığı olan 20 adet hayvana tek doz 2.5 mg/kg tulathromycine (grup 1) ve diğer 20 adet hayvana 10 mg/kg tilmicosin (grup 2) tek doz derialtı yolla uygulandı. Tulathromycin uygulanan grup 1'in hayvanlarında beş gün içerisinde iyileşme oranı %85, tilmicosin uygulanan grup 2'deki hayvanlarda ise %80 olarak tespit edildi. Sonuç olarak, bovine respiratory disease hastalığının tedavisinde hem tulathromycin hemde tilmicosinin etkili olduğu belirlendi.

Anahtar Kelimeler *Solunum sistemi hastalığı,Etiyoloji, Tulathromycin, Tilmicosin,, Tedavi*

INTRODUCTION

Bovine respiratory disease (BRD) is an important cause of mortality and morbidity in cattle (Bryson1985; Ames 1997; Loneragan et al. 2001). The condition involves a complex of different etiologies, including various viral, mycoplasmal, and bacterial pathogens, and susceptibility is potentiated by stresses arising from the environment, inadequate ventilation, poor housing, poor nutrition, high stocking density, and transportation (Bryson1985; Knowles 1995; Ames 1997;).

In clinical outbreaks of BRD, primary or secondary bacterial infections are frequently implicated in cases with a severe clinical presentation; these infections are related to the underlying pathologic changes in the lungs. Common bacterial pathogens associated with BRD include *P. haemolytica*, *P. multocida*, *H. somni* and *Mycoplasma* spp., with *M. haemolytica* considered the primary bacterial pathogen. BRD is a multifactorial disease complex with clinical presentations ranging from subclinical to severe acute bronchopneumonia (Donachie 2000; Loneragan et al. 2001; Nicholas and Ayling 2003). Macrolide compounds, such as erythromycin, clarithromycin, and the azalide azithromycin, are generally effective in the treatment of respiratory disease in both laboratory models and clinical infections in humans (Veber et al. 1993; Zhanel et al. 2001). Tulathromycin is a recently developed triamilide antimicrobial, distinguished from other macrolides by the presence of three polar amine groups in the molecule (Letavic et al. 2002; Kilgore et al. 2005). Macrolides such as tylosin and its semisynthetic derivative

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tilmicosin have been developed for and to determine the efficacy of tulathromycin in the prevention of clinical signs of BRD when administered metaphylactically to in contact animals (Ames 1997; Godinho 2005; Godinho 2005).

Tilmicosin has been extensively used for the control of respiratory disease in cattle at high risk of developing BRD, partially because of its single dose administration and duration of activity (Apley 1997). Tulathromycin has shown in vitro activity against bacterial pathogens involved in BRD (Norcia et al. 2004). Pharmacokinetic studies of tulathromycin administered at 2.5 mg/kg have demonstrated excellent bioavailability, with rapid absorption followed by extensive distribution into lung tissues and a half-life in lung tissue of approximately 8 days (Nowakowski et al. 2004). The extended period of slow decline in lung concentrations of tulathromycin results in a prolonged period of antimicrobial exposure to bacterial pathogens at the site of infection (Nowakowski et al. 2004).

The objective of this study was to investigate bacterial etiology and to compare the clinical effects of tulathromycin and tilmicosin in the treatment of respiratory system diseases in cattle.

MATERIALS and METHODS

Animals

This study involved 40 mixed-breed, 8-14 months old, weighting 300-500 kg male cattle with bronchopneumonia. All animals were subjected to similar management conditions. A complete physical examination was performed on each animal. The diagnosis of bronchopneumonia was based on clinical symptoms and microbiological examinations. Diseased animals showed all clinical signs of pneumonia, fever, cough, nasal flaring, anorexia, dyspnea, dullness.

Clinical examination

Appetite, rectal temperature, pulse rate and respiratory rate of all animals included in the study were observed for five days.

Microbiological examination

Deep nasopharyngeal swabs for the identification of respiratory pathogens were obtained from 40 animals before the treatment (Day 0). Bacteriological isolation Blood Agar, Mac Conkey Agar, Mycoplasma Selective Broth and Mycoplasma Selective Agar are used.

Aerobic growth medium and 10% in sowing the CO_2 in the atmosphere were incubated 24-72 hours. Pasteurella colonies suspected to have seen the end of incubation, colony morphology, haemolysis and staining properties were examined, then Indole, β-galactosidase, H_2S and identification using lactose testing was performed.

Treatment

Animals with pneumonia included in the study were divided into two equal groups. Animal in group I (n=20) received a single dose of tulathromycin (Draxxin® Pfizer, 2.5 mg/kg SC) and animals in group II 2 (n=20) were given single dose of tilmicosin (Micotil® Elanco, 10 mg/kg SC). The clinical examinations were evaluated following treatment for five days.

Statistical analysis

Data were analyzed using SPSS 16.0 statistical package program (SPSS Inc, Chicago, Illinois USA). An independent samples t-test was used to reveal the statistical significance between the two groups. Statistical significance was considered to be $P<0.05$. The results are expressed as means ± standard deviations.

RESULTS

Clinical findings

Changes in rectal temperature, pulse rate and respiration rate of animals during 5 days of treatment with tulathromycin and tilmicosin are given in Table 1.

Seventeen animals in group 1 began to recover on the fourth day of treatment but 3 animals still had dyspnea, cough, pathological lungs sounds and anorexia. Similarly, 16 out of 20 animals in group 2 began to recover on the fourth day of treatment and 4 animals still had dyspnea, cough, pathological lungs sounds and anorexia.

In this study, rectal temperature, pulse and respiration rate of animals in both groups decreased starting on the first day of treatments. Differences in body temperature on the second day, in pulse frequencies on the first, second, fourth and fifth days and in respiration rates on the first, third, fourth and fifth days were found to be statistically significant ($P<0.05$) (Table 1). Appetite of recovered animals improved on the fourth day in both groups. Recovery rate in five days was determined as 85% in group 1 and 80% in group 2 (Table 2).

Table 1. The effects of tulathromycin (Group 1) and tilmicosin (Group 2) on mean rectal temperature, pulsation rate and respiratory rate before and after treatment.

Tablo 1. Tedavi öncesi ve tedavi sonrası tulathromycin (Grup 1) ve tilmicosin (Grup 2)'de rektal ısı, nabız ve solunum sayıları

Parameters	Groups	Days					
		B.T.	1	2	3	4	5
Temperature °C	I	40.1±0.5	38.9±0.2	38.9±0.2[a]	38.8±0.2	38.7±0.2	38.6±0.3
	II	39.9±0.5	39.1±0.5	38.6±0.3[b]	38.7±0.3	38.7±0.3	38.7±0.4
Pulsation rate/min.	I	72.9±4.6	69.4±4.7[a]	66.9±3.1[a]	66.9±3.1	65.3±3.1[a]	66.0±2.7[a]
	II	70.1±4.1	65.5±3.4[b]	64.7±2.5[b]	65.2±2.8	63.3±2.8[b]	61.7±2.8[b]
Respiration rate/min.	I	57.6±5.4	51.8±3.6[a]	42.8±4.2	40.1±4.8[a]	39.3±4.2[a]	37.3±3.4[a]
	II	55.3±6.8	48.0±5.0[b]	44.3±5.6	44.3±4.5[b]	42.2±4.0[b]	40.5±4.5[b]

Statistically significant between groups: : [a,b] $p<0.05$ B.T. : Before treatment

Table 2. Efficacy of tulathromycin versus tilmicosin for the treatment of cattle with BRD.

Tablo 2. BRD'li sığırların tedavisinde tulathromycin ve tilmicosinin etkisi

Treatment Group	Study period	Number (%) of Cattle	
		Group-1	Group-2
Recovered	Day 1-5	17 (85)	16 (80)
Morbidity	Day 1-5	3 (15)	4 (20)

Microbiological findings

P. haemolytica 6 (30%), *P. multocida* 4 (20%), *P. haemolytica + streptococcus spp.* 2 (10%), *P. multocida + streptococcus spp.* 1 (5%), *streptococcus spp.* 1 (5%) and *K. pneumonia* 2 (10%) were isolated from the animals treated with tulathromycin (Group 1, n: 20) (Table 3) no isolation was made from 4 animals. On the other hand, *P. haemolytica* 5 (25%), *P. multocida* 5 (25%), *P. haemolytica + streptococcus spp* 2 (10%), *P. multocida + Streptococcus spp.* 1 (5%), *Streptococcus spp.* 1 (5%) and *K. pneumonia* 2 (10%) were isolated from the animals treated with tilmicosin (Group 2, n: 20) (Table 3); however, no bacterium was isolated from 4 animals.

Table 3. Bacterial pathogen isolated and identified from cattle wit BRD

Tablo 3. BRD'li sığırlardan izole ve identifiye edilen bakteriler

Isolates	Number (%) of cattle with positive cultures	
	Group 1	Group 2
Pasteurella haemolytica	6 (30)	5 (25)
Pasteurella multocida	4 (20)	5 (25)
Pasteurella haemolytica + Streptococcus spp	2 (10)	2 (10)
Pasteurella multocida + Streptococcus spp	1 (5)	1 (5)
Klebsiella pneumonia	2 (10)	2 (10)
Streptococcus spp	1 (5)	1 (5)

DISCUSSION

Bacterial pathogens play an important role for the etiology of BRD in cattle (Gökçe et al. 1997; Loneragan et al. 2001; Booker et al. 2007; İçen et al. 2009;). Gökçe et al. (1997) determined that 56.6% *P. multocida* and *P. haemolytica*, 23.3% *K. pneumonia, Staphylococcus spp*., and *Candida* were isolated from nasal swabs samples collected from calves. İçen et al. (2009) determined that *M. haemolytica, K. pneumoniae,* Coagulase (+) *Staphylococcus* and *Streptococcus spp*. were isolated from nasal swabs and blood samples collected from beef calves. The researcher Picavet et al. (1991), Booker et al. (1997) and Loneragan et al. (2001) reported that *P. haemolytica*, *P. multocida, K. pneumonia, M. bovis, S. bovis*, *H. somnus* were isolated from calves with bronchopneumonia. In the present study, *P. haemolytica* 27.5%, *P. multocida* 22.5%, *K. pneumonia* 10%, *P. haemolytica + streptococcus spp.* 10%, *P. multocida + streptococcus spp*. 5%, *Streptococcus spp.* 5% out of total 40 samples were isolated (Table 3). The data reported here support the findings of this study.

The first clinical signs observed in calves affected anorexia, rapid and labored breathing, dyspnea, abnormal lung sounds, mandibular lymph node enlargement and cough, nasal and ocular discharge, fever (Gökçe et al. 1997; Skogerboe 2005; İçen et al. 2009). İçen et al. (2009) reported that there were significant improvement in the distribution of clinical signs for abnormal respiration ($P<0.001$, $P<0.005$, $P>0.005$), pulsation ($P<0.001$, $P<0.001$, $P<0.001$) and depression on day 3 and 7 compared to day 0.

In the study, body temperature, pulse and respiration rate of animals in both groups were observed to be decrease from the first day of the treatments. For both groups of animals, differences in body temperature on the second day, in pulse frequencies on the first, second, fourth and fifth days and in respiration rates on the first, third, fourth and fifth days were found statistically significant ($P<0.05$) (Table 1). Appetite of healed animals improved on the fourth day in both groups. These findings were in accordance with previous studies (Loneragan et al. 2001; Godinho et el. 2005; Godinho et al. 2005; İçen et al. 2009).

Bovine respiratory disease (BRD) is considered the most costly disease in the beef cattle industry. Respiratory disease is generally regarded as the most frequent and serious cause of mortality associated with the feedlot industry (Kelly and Janzen 1986; Mosier 1997). Economic losses are more than just death. To treat BRD, it is very important to focus not only on prevention, but also to fight the bacteria that complicate the viral infections (Booker et al. 2007).

Godinho et al. (2005) reported that in the efficacy of tulathromycin in the treatment and prevention of bovine respiratory disease (BRD) was evaluated on commercial farms in France, Germany, Italy, and Spain. Significantly more ($P<0.001$) cattle treated with tulathromycin remained healthy to day 14 (92.4%) than cattle treated with tilmicosin (83.7%) or saline (63.7%), and this was maintained through day 60 (85.4% for tulathromycin versus 75.1% for tilmicosin and 56.2% for saline). Tulathromycin was highly effective in the treatment and prevention of BRD. Robb et al. (2007) reported that after undergoing arrival processing at one of two commercial feedlots, feeder calves with clinical signs of bovine respiratory disease (BRD) were randomly assigned to receive either tulathromycin (2.5 mg/kg SC) or enrofloxacin (12.5 mg/kg SC). Initial treatment with tulathromycin resulted in significantly higher therapeutic success (87.9% and 80%, respectively) than did initial treatment with enrofloxacin (70.2% and 62.5%, respectively). Skogerboe et al. (2005) reported that cure rate, a derived variable that included assessments of mortality, rectal temperature, and attitude and respiratory scores from day 3 to day 28 and day 3 through harvest, was the primary assessment of BRD efficacy. Cure rates of calves treated with tulathromycin were significantly higher than those calves treated with florfenicol. The cure rate of calves treated with tulathromycin was significantly higher compared with tilmicosin treated calves. Tulathromycin was more efficacious in the treatment of undifferentiated BRD compared with florfenicol and, in one study, compared with tilmicosin.

Antimicrobial treatment is the most effective method for the prevention and management of pneumonia. Tulathromycin, tilmicosin was approved for the treatment of pneumonia and for the reduction of morbidity in calves in Turkey and around the world (Skogerboe et al. 2005; Robb et al. 2007; Schunicht et al. 2007).

İçen et al. (2009) clinical measures of efficacy included mortality, rectal temperatures, pulsation, respiratory rate, assessment of treatment success or failure and number of relapses. Four calves relapse and needed second injection.

No significant adverse reactions were noticed with tulathromycin. After the treatment, all the calves were cured. Gökçe et al. (1997) determined respiration difficulty, cough and pathological sounds in lungs, anorexia in a calf at the end of the fifth day. They reported that 14 animals began healing from the fourth day of treatment. Their reached 93% of success rate with one dose of tilmicosin. They reported slight cough in 3 calves despite the normal appetite. This study, body temperature, pulse frequency and respiration rate were reported to be reduced from the first day of treatment; in addition, 85% of the animals in group 1 and 80% of animals in group 2 were healed at the end of the fifth day, which were found compatible with the results of previous researchers (Godinho et al. 2005; Gökçe et al. 1997; İçen et al. 2009; Robb et al. 2007; Skogerboe et al. 2005).

In conclusion; *P. haemolytica* 27.5%, *P. multocida* 22.5%, *P. haemolytica + Streptococcus spp.* 10%, *P. multocida + Streptococcus spp.* 5%, *K. pneumonia* 10% and *Streptococcus spp*. 5% were isolated from the animals included in this study. Recovery rate of the animals with pneumonia was determined as 85% in the group treated with tulathromycin and 80% in the other group treated with tilmicosin. The results of this study indicate that tulathromycin, administered once, SC, at the rate of 2.5 mg/kg body weight (BW), is more effective for the treatment of the respiratory system diseases in cattle than tilmicosin, administered once, SC, at the rate of 10 mg/kg BW, due to its higher recovery rates. Both tulathromycin and tilmicosin administration were found to be effective in the treatment of bovine respiratory disease of cattle.

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