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Viral and Bacterial Pathogen Isolated and Identified from Pneumonic Calves in Region of Diyarbakir and its Treatment with Tulathromycin

[1]Hasan Icen, [1]Servet Sekin, [2]Simten Yesilmen, [3]Nurettin Isik and [1]Aynur Simsek
[1]Department of Internal Medicine, [2]Department of Microbiology,
Faculty of Veterinary Medicine, University of Dicle, 21280 Diyarbakir, Turkey
[3]Laboratory of Research, Diagnosis and Control of Animal Diseases, Diyarbakir, Turkey

Abstract: We tested the field efficacy of a new antibiotic tulathromycin in the treatment of naturally occuring bovine respiratory disease beef calves with rectal temperatures >39.5°C and signs compatible bovine respiratory disease were entered into the trial. This study was performed on 30 mixed-breed beef calves with bronchopneumonia, 8-10 months old. Bacteriological and serological examinations were performed in nasal swabs and blood samples collected from beef calves. *Klebsiella pneumoniae*, *Mannheimia haemolytica*, Coagulase (+) *Staphylococcus* and *Streptococcus* sp. were isolated from bacteriological examinations of bronchoalveolar lavage. Serum samples were tested serologically for antibodies to Infectious bovine rhinotracheitis, Parainfluenza-3, Bovine adenovirus and Bovine viral diarrhea viruses. All samples were positive for antibodies to Infectious bovine rhinotracheitis, Parainfluenza-3, Bovine adenovirus and Bovine viral diarrhea viruses. Calves were assigned to receive tulathromycin (2.5 mg kg^{-1} bodyweight, subcutaneously). Clinical measures of efficacy included mortality, rectal temperatures, pulsation, respiratory rate, assesment of treatment succes or failure and number of relapses. Four calves relapses and needed second enjection. No significant adverse reactions were noticed with tulathromycin. After the treatment, all the calves were cured. Results indicate that tulathromycin administration was found to be effective in the treatment of bovine respiratoy diseases (especially in bacterial infections) of beef calves in region of Diyarbakir.

Key words: Pneumonia, beef calves, tulathromycin, Diyarbakir, nasal swabs, blood samples

INTRODUCTION

Losses due to Bovine Disease (BRD) respiratory are among the most important health problems encountered the of feedlot calves during fattening (Harland *et al*., 1991; Hartel *et al*., 2004; Hodgson *et al*., 2005). The Bovine Respiratory Diseases result from the interaction of many pathogenic agents (virus, mycoplasmes and bacteria) and other aggressions like a concomitant disease, the stress related on the mixture and the transport of the animals at the time of regroupings such as the markets with the cattle, of the climatic or environmental conditions unfavourable (defective ventilation, for example), or of the unsuited conditions of breeding like a high density or a bad food (Hoar *et al*., 1998; Hodgson *et al*., 2005; Godinho *et al*., 2005a, b). The viruses cause the early phase of the disease and will further reduce the natural disease resistance of the upper airways (Poumarat *et al*., 2001; Akdogan *et al*., 2001; Rowan *et al*., 2004). Bovine Respiratory Syncytial Virus (RSV), Parainfluenza 3 (Pi3) and the IBR virus are the ones of importance. Bovine Viral Diarrhea virus (BVD) does not damage the respiratory tract but lowers the immunity of the calves and so makes them more susceptible to the effects of the other infections (Loneragan *et al*., 2001). The pathogenic agents *Mannheimia* (*Pasteurella*) *haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*) or *Streptococcus pneumonia*, *Klebsiella pneumoniae* and either alone or with viruses and or, *Mycoplasma bovis*, are the most common microorganisms isolated in case of BRD (Booker *et al*., 1997; Lekeux and Art, 1988; Cimtay *et al*., 2000; Thomas *et al*., 2001).

The initial symptoms of the disease include pyrexia, coughing, ocular and nasal discharge. The occurrence of anorexia, tachypnoea and dyspnoea indicates a more serious in BRD (Larsen *et al*., 2001).

Antimicrobial therapy is the most effective method for the prevention and treatment of BRD. Treatments utilizing various antibacterials frequently are administered daily for several consecutive days. If response to the first

Corresponding Author: Hasan Icen, Department of Internal Medicine, Faculty of Veterinary Medicine, University of Dicle, 21280 Diyarbakir, Turkey

antibacterial is poor, a second antibiotic may be administered for another 2-3 days. Such a program is labor intensive because of the daily handling and stressful to the cattle due to the restraint involved (Gorham *et al*., 1990). The antimicrobial agents commonly used to treat BRD include ampicillin, ceftiofur, enrofloxacin, florfenicol, marbofloxacin, tilmicosin erythromycin, oxytetracycline, spectinomycin and sulfamethazine (Akgul *et al*., 1995; Booker *et al*., 1997; Lekeux and Art, 1988; Thomas *et al*., 2001; Hibbard *et al*., 2002). However, previous studies have indicated that resistance to these compounds is frequently encountered. Currently, several new antimicrobial agents have been introduced or are under development for the treatment of BRD. An antibacterial treatment, which could be administered as a single injection would offer numerous advantages.

The efficacy of a single dose of 2.5 mg kg^{-1} b.w. tulathromycin has been sufficiently demonstrated for the treatment and prevention of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Haemophilus somnus* and the efficacy in the treatment of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Mycoplasma hyopneumoniae* by the improvement of the clinical signs of the disease. Also, the efficacy of tulathromycin was demonstrated to be comparable to that of an already approved veterinary medicinal products containing tilmicosin (BRD), tiamulin (SRD) or florfenicol (SRD) (Godinho *et al*., 2005a, b; Schunicht *et al*., 2007; Booker *et al*., 2007).

The purpose of this clinical trial was to obtain basic knowledge of pathogens associated with bovine respiratory disease in Diyarbakir and evaluate single injection dosages of tulathromycin for treatment of naturally occurring BRD in feedlot calves.

MATERIALS AND METHODS

This study was performed on 30 mixed-breed beef calves with bronchopneumonia, the age of the diseased calves varied from 8-10 months and the weights were between 50 and 100 kg.

The animals were clinically examined by the same investigator on D0, D3 and D7, for rectal temperature (°C), respiratory rate, general condition, dyspnea, nasal discharge, ocular discharge, bilateral conjunctivitis, abnormal lung sounds, mandibular lymph node enlargement and cough. All of the calves had abnormal sounds on auscultation of the respiratory tract and most had either one or several of the following symptoms: fever >39.5°C, elevated respiratory rate (>40 min^{-1}), cough or nasal discharge. On day 0, deep nasopharyngeal swabs for the identification of respiratory pathogens were obtained from 11 animal before it was treated. Blood samples for serology were taken from 11 calves. Blood was collected into sterile vacutainers by jugular venipuncture. Sera were separated and stored at -20°C until required for testing blood samples collected from beef calves. For bacteriological isolation Blood Agar, MacConkey Agar No. 2, Mycoplasma Selective Broth, Mycoplasma Selective Agar are used. Biochemical identifications of izolated Gram negative bacterias was carried out according to API20E, but Gram positive bacterias was identified biochemically according to Bergeys Manuel of Systematic Bacteriology; *Klebsiella pneumoniae*, *Mannheimia haemolytica*, Koagulase (+) *Staphylococcus* and *Streptococcus* sp. were isolated from bacteriological examinations of bronchoalveolar lavage.

The virus neutralization tetst was used to determine antibodies to Bovine Herpes Virus 1 (BHV1), Infectious Bovine Rhinotracheitis (IBR), Bovine Viral Diarrhea (BVD) virus and Bovine Respiratory Syncytial Virus (BRSV). The hemaglutination inhibition test was used for antibodies to bovine parainfluenza virus according to standard protocol.

A single dose of 2.5 mg kg^{-1} b.w. tulathromycin were administered subcutaneusly to the diseased calves. The clinical examination were carried out following treatment of 3rd and 7th days. Total 72 h later they were given a second dose of danofloxacin if they had either a rectal temperature of at least 39.5°C or moderate or severe clinical signs of abnormal respiration or depression.

The one-way ANOVA test was performed in order to compare the three groups for each of the evaluated parameters. The data on the clinical signs, pulses, respiratory rate and the rectal temperatures were analyzed only for the animals. the statistical differences in the tulathromycine group between D0 and D3 and D7. A difference with $p<0.05$ was considered to be significant. All statistical analyses were performed with statistics package SPSS version 13.0 (SPSS inc).

RESULTS

Rectal temperature, respiratory rate, appetite, dyspnea, coughing, nasal discharge and general condition were recorded on days 0, 3 and 7. The clinical efficacy of tulathromycin were evaluated on days 3 and 7. Mean, standard deviation and differences in values of parametres obtained in the research are given on the Table 1 and 2.

For animal completing the study the mean rectal temperature on day 0 was 40.2°C. On 3rd day rectal temperature had reduced to 39.6°C and reduction was sustained throught to day 7 when the mean rectal

Table 1: Tempurature, respiratory rate and pulsation rate of pneumonic calves before (0 day) and after (3 and 7 day) application of tulathromycin

Parameters	0 day	3 days	7 days	N = 30 (p-value)
Tempurature	40.28±0.63	39.0±0.63***	38.6±0.36***	0-3 (<0.001)
				0-7(<0.001)
				3-7 (<0.001)
Respiratory rate	46.53±9.56	25.20±7.65***	22.20±3.16*	0-3 (<0.001)
				0-7 (<0.05)
				3-7 (>0.05)
Pulsation	110.80±11.49	89.86±11.05	79.73±4.38	0-3 (<0.001)
				0-7 (<0.001)
				3-7 (<0.001)

Table 2: Clinical findings of pneumonic calves pre treatment (0 day) and after treatment (3 and 7 day) and application of tulathromycin

Nasal discharge			Cough			Conjunctiva			Rumen moving			Lung auskultastion			Tulathromycin (2.5 mg kg^{-1}) S.C		
0 day	3 day	7 day	0 day	3 day	7 day	0 day	3 day	7 day	0 day	3 day	7 day	0 day	3 day	7 day	0 day	3 day	7 day
SM	SM	-	+	-	-	H	N	N	2	5	11	DR	DR	N	+		
SM	N	-	+	-	-	H	N	N	2	7	12	DR	N	N	+		
SM	N	-	+	-	-	H	N	N	4	9	10	MR	N	N	+		
SM	N	-	+	-	-	H	N	N	3	7	9	MR	N	N	+		
SM	N	-	+	-	-	H	N	N	5	11	13	DR	N	N	+		
S	N	-	-	-	-	H	N	N	5	13	12	HV	N	N	+		
SM	SM	-	+	-	-	H	N	N	3	9	14	MR	DR	N	+		
SM	N	-	+	-	-	H	N	N	2	8	11	DR	N	N	+		
SM	SM	-	+	-	-	H	N	N	2	11	12	DR	DR	N	+	+	
S	N	-	+	-	-	H	N	N	4	10	12	HV	N	N	+		
S	N	-	-	-	-	H	N	N	3	9	13	HV	N	N	+		
SM	N	-	+	-	-	H	N	N	2	6	11	MR	N	N	+		
S	N	-		-	-	H	N	N	5	8	10	HV	N	N	+		
S	N	-	+	-	-	H	N	N	4	11	13	HV	N	N	+		
SM	SM	-	+	-	-	H	N	N	3	8	11	MR	N	N	+		
SM	SM	-	+	+	-	H	N	N	1	6	10	DR	DR	N	+	+	
SM	N	-	+	-	-	H	N	N	2	9	12	DR	N	N	+		
SM	N	-	+	+	-	H	N	N	2	9	14	DR	N	N	+		
M	N	-	-	-	-	H	N	N	5	14	13	HV	N	N	+		
SM	N	-	+	-	-	H	N	N	3	9	12	MR	N	N	+		
SM	N	-	+	-	-	H	N	N	2	8	13	MR	N	N	+		
SM	N	-	+	-	-	H	N	N	2	9	11	MR	N	N	+		
SM	N	-	+	-	-	H	N	N	3	11	14	MR	N	N	+		
S	N	-	+	-	-	H	N	N	4	7	12	HV	N	N	+		
SM	N	-	+	-	-	H	N	N	2	8	11	DR	N	N	+		
M	N	-	-	-	-	H	N	N	5	9	13	HV	N	N	+		
M	N	-	-	-	-	H	N	N	5	11	12	HV	N	N	+		
SM	N	-	+	-	-	H	N	N	2	6	11	DR	N	N	+		
SM	N	-	+	+	+	H	N	N	2	8	13	DR	N	N	+	+	
SM	SM	-	+	+	+	H	N	N	1	7	12	DR	DR	N	+	+	

SM: Seromucous, S: Serous, M: Mucous, N: Normal, H: Hyperemia, DR: Dry Rale, MR: Moist Rale, HV: Hard Vesicoul

Table 3: Viral and bacterial pathogen isolated and identified from pneumonic calves

		Viral antibody				
A.N	Bacterial pathogen isolated and identified	BRSV	PI-3	IBR	BVD	Adenovirus
1	*Klebsiella pneumoniae*, *Mannheimia haemolytica*	Positive	Positive	Positive	Positive	Negative
3	*Klebsiella pneumoniae*, *Mannheimia haemolytica* *Satphylococcus* sp.	Positive	Positive	Positive	Negative	Negative
9	*Klebsiella pneumoniae*, *Mannheimia haemolytica*	Positive	Positive	Positive	Positive	Negative
12	*Mannheimia haemolytica* *Streptococcus* sp.	Positive	Positive	Positive	Negative	Negative
14	*Mannheimia haemolytica*	Positive	Positive	Positive	Negative	Positive
15	*Mannheimia haemolytica*	Positive	Positive	Positive	Negative	Positive
16	*Streptococcus* sp. *Mannheimia haemolytica*	Positive	Positive	Positive	Positive	Negative
21	*Mannheimia haemolytica*	Positive	Positive	Positive	Negative	Negative
24	*Klebsiella pneumoniae*,	Positive	Positive	Positive	Positive	Negative
27	*Klebsiella pneumoniae*, *Staphylococcus* sp.	Positive	Positive	Positive	Positive	Negative
29	*Klebsiella pneumoniae*, *Mannheimia haemolytica* *Staphylococcus* sp.	Positive	Positive	Positive	Positive	Negative

temperature were 38.6°C. The reduction between rectal temperatures on days 3 and 7 compared with day 0 were significant differents ($p<0.001$). There were significant improvement in the distrubition of clinical signs for abnormal respiration ($p<0.001$, $p<0.005$, $p>0.05$), pulsation ($p<0.001$, $p<0.001$, $p<0.001$) and depression on day 3 and 7 compared to day 0. Four of 30 beef calves recevied second enjection for treatment.

Klebsiella pneumoniae, *Mannheimia haemolytica*, Koagulase (+) *Staphylococcus* and *Streptococcus* sp. were isolated from bacteriological examinations of bronchoalveolar lavage.

Serological examination to viruses, Bovine Herpes Virus 1 (BHV1), Infectious Bovine Rhinotracheitis (IBR), Bovine Viral Diarrhea (BVD) virus and Bovine Respiratory Syncytial Virus (BRSV) were determined (Table 3).

DISCUSSION

BRD is a very costly disease to cattle producers. 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).

The first clinical signs observed in calves affected yere anorexia, rapid and labored breathing, dyspnea, abnormal lung sounds, mandibular lymph node enlargement and cough, nasal and ocular discharge, fever. There were significant improvement in the distrubition of clinical signs for abnormal respiration ($p<0.001$, $p<0.005$, $p>0.05$), pulsation ($p<0.001$, $p<0.001$, $p<0.001$) and depression on day 3 and 7 compared to day 0. These findings were in accordance with previous studies (Akgul *et al*., 1995; Cimtay *et al*., 2000; Akdogan *et al*., 2001; Godinho *et al*., 2005a, b).

The animal's normal bodily defenses keep these bacteria in check in a healthy animal, they replicate slowly, are destroyed by antibodies and removed by macrophages. Respiratory tract infections (pneumonia) due to these two bacteria occur when the organism is inhaled. Under conditions of impaired pulmonary defenses, a severe necrotizing fibrinous pneumonia develops. Spread of these organisms is by direct contact, or by ingestion of feed and water contaminated by nasal and oral discharges from infected cattle (Hoar *et al*., 1998; Hartel *et al*., 2004; Hodgson *et al*., 2005). The severity of the disease depends upon the pathogenicity of the bacterial organism (s) and the associated Infections (IBR, PI-3, BVD and BRSV, other viruses or bacteria). *M. haemolytica* is often associated with the more acute cases of BRD, while, *P. multocida* is often associated with the longer-lasting cases of BRD. Therefore, these two bacteria are easily spread between cattle, especially when calves are crowded (as in shipment) or closely confined (as in a dairy calf nursery) (Irsik and DVM, 2008).

The researcher Picavet *et al*. (1991), Booker *et al*. (1997) and Loneragan *et al*. (2001) reported that *Klebsiella pneumoniae*, *P*. (Mannheimia) *haemolytica*, *P. multocida*, *M. bovis*, *Strept. bovis*, *Haemophilus somnus* were isolated from calves with bronchopneumonia. The data reported here support our finding. Bacteria isolated during our studies are classically considered to contribute to the pathology of BRD complex. In serological examination of virus in this study were Bovine Herpes Virus 1 (BHV1), Infectious Bovine Rhinotracheitis (IBR), Bovine Viral Diarrhea (BVD) virus and Bovine Respiratory Syncytial Virus (BRSV). Similarly, findings were reported by Godinho *et al*. (2005a, b), Loneragan *et al*. (2001), Gorham *et al*. (1990), Schunicht *et al*. (2007), Booker *et al*. (2007) and Robb *et al*. (2007).

Many of the antibiotics used in the treatment of BRD, particularly to give protection to incontact animals, are long acting formulations with very long statutory withdrawal periods. A recently launched new product, containing Tulathromycin (Draxxin® Pfizer) has been marketed to veterinarians as suitable for treatment of BRD. Early administration of an effective antimicrobial at the appropriate dose is beneficial for the successful treatment of BRD-affected animals. The most common antimicrobials used by feedlots for the initial treatment of respiratory disease were tilmicosin, florfenicol and tetracyclines. Akdogan *et al*. (2001) reported that combination of Parapoxvirus with Enrofloxacine resulted in more effective therapy than the Enrofloxacine monotheraphy in the treatment of calves with enzootic pneumoniae.

Kilgore *et al*. (2005a, b), Rooney *et al*. (2005) and Nutsch *et al*. (2005) reported that tulathromycin given to calves at high risk of developing BRD was significantlY more effective in reducing BRD morbidity and mortailty compared with florfenicol and tilmicosin.

The complete reversibility of the clinical and functional changes recorded in the diseased calves suggests that most of the microrganisms involved in the pathological effects on the respiratory tract were sensitive to tulathromycine. This is in agrement with previous reports.

In this study, a single dose of 2.5 mg kg^{-1} b.w. tulathromycin were administered subcutaneusly to the diseased calves. On the 3rd day four calves (13.5%) relapses and needed second enjection. No significant adverse reactions were noticed with tulathromycin. All the beef calves were cured. These findings are consisted with the literature data (Godinho *et al*., 2005a, b; Skogerboe *et al*., 2005; Schunicht *et al*., 2007; Booker *et al*., 2007; Robb *et al*., 2007).

CONCLUSION

The tulathromycine can being used not only in the treatment of the respiratory disorders, but also in the prevention of the appearance of clinical signs of broncho-pneumonopathies in the animals sharing same space.

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