Comparison of enrofloxacin and tulathromycin treatments in sheep with pneumonia caused by *Pasteurella multocida*

ABSTRACT

The objective of the present study was to compare the treatments of enrofloxacin and tulathromycin in sheep with pneumonia caused by *Pasteurella multocida*. A total of 45 female Tuj sheep between the of 2-6 years old were used in the study. Group 1 enrofloxacin administered 15 sheep, group 2 tulathromycin administered 15 sheep, and 15 healthy sheep of the same age group and characteristics enrolled in the study. Bronchoalveolar lavage fluid samples were obtained from sheep with clinical signs (cough, purulent, serous, mucopurulent nasal discharge) of respiratory system disease. After the microbiological examination of the taken samples, those were positive for Pasteuralla multocida included in the study. Blood samples (10 mL) from the *Vena jugularis* were collected in serum tubes with K_2EDTA and gel from the sick animals before and after the treatment as well as once from the control group. In our study, rectal temperature, respiratory rate and heart rate before treatment were found to be statistically significantly higher in patient groups compared to the control group ($P<0.001$). Total leukocyte count was found to be higher in the patient groups before treatment compared to the control group ($P=0.010$). Among the biochemical parameters, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urea and creatine kinase levels were found to be statistically significantly higher in the patient groups compared to the control group before treatment ($P<0.05$). Clinical improvement was observed from the 3th day in group 2 and from the 5th day in group 1. In conclusion, administration of a single dose of tulathromycin resulted in earlier clinical improvement than administration of enrofloxacin for one week. At the same time, it was concluded that tulathromycin is more beneficial and practical in terms of a single application.

Keywords: Enrofloxacin, *Pasteurella multocida*, sheep, tulathromycin, tuj.

INTRODUCTION

The term pneumonia is the name given to lung inflammation caused by different etiological factors (Dağ et al., 2018; Eser et al., 2020). Age, breed, immune status and environmental factors have an effect on the emergence of some diseases in sheep (Gülmez et al., 2018). Respiratory system diseases are clinically acute, subacute and chronic. Viral, bacterial, mycotic and parasitic factors play a role in its etiology. Depending on where the inflammation is localized, it progresses as bronchopneumonia, lober and interstitial pneumonia (Çiftçi et al., 2015). In addition to the infectious causes in the etiology, climate changes, cold, stress, bad barn conditions, transport and malnutrition are the main factors that predispose to the disease (Issi et al., 2015). Pneumonia seen in sheep is common in our country as well as all over the world. Respiratory system infections have a share of 5.6% among the diseases seen in sheep. The type of pneumonia seen in sheep is a fibrinous and necrotic bronchopneumonia (Eser et al., 2020).

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Research Article

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Pasteurella, caused by *Pasteurella multocida* (*P. multocida*) and *Mannheimia haemolytica* (*M. haemolytica*), usually manifests as a respiratory infection in small farm-raised ruminants and causes significant economic losses worldwide. *P. multocida* is rarely mentioned in pneumonia outbreaks in small ruminants. Infectious *P. multocida* sero groups associated with pneumonic pasteurellosis outbreaks in sheep and goats are groups A and D, which have been shown to be both secondary and primary pneumonia agents (Odugbo et al., 2006).

Developed for veterinary medicine and approved for use in animals in the late 1980s, enrofloxacin in the first fluoroquinolone group is used in septic shock, gastrointestinal, urogenital, respiratory, dermal, mycoplasma and staphylococcal infections in ruminant, equidae, poultry, dogs, cats, and exotic animals (Martinez et al., 2006; Traş et al., 2018). Enrofloxacin can be used in diarrhea caused by *E. coli*, pneumonia caused by *Actinobacillus pleuropneumoniae*, mycoplasma and pasteuralla (Nakamura, 1995). Tulathromycin is approved for use in the treatment and prevention of respiratory tract disease in cattle associated with *M. haemolytica*, *P. multocida*, Histophilus somni and *Mycoplasma bovis* in the United States (Villarino et al., 2014). Apart from cattle and pigs, it can be used for antimicrobial purposes in horses, goats and sheep (Sirochman et al., 2012; Villarino et al., 2013). When administered in a single dose of 2.5 mg/kg (SC) in sheep, it may be safe in terms of heart, liver, kidney and hematological parameters in sheep (Çorum et al., 2015).

The objective of the present study was to compare the treatments of enrofloxacin and tulathromycin in sheep with pneumonia caused by *P. multocida.*

MATERIAL and METHOD

Animals

The study was carried out at Kafkas University, Faculty of Veterinary Medicine, Prof. Dr. Ali Rıza Aksoy Training, Research and Application Farm in Kars. A total of 45 female Tuj sheep between the of 2-6 years old were used in the study. Bronchoalveolar lavage fluid (BALf) samples were obtained from sheep with clinical signs (such as cough, purulent, serous, mucopurulent nasal discharge) of respiratory system disease. After the microbiological examination of the BALf taken samples, those were positive for *P. multocida* included in the study. Group 1 consists of 15 sheep with pasteurellosis that were administered enrofloxacin (Baytril 10%®, Bayer, Germany, 5 mg/kg intramuscularly for 1 week). Group 2 consists of 15 sheep with pasteurellosis that were administered tulathromycin (Draxxin®, Zoetis, USA, 2.5 mg/kg single dose intramuscularly). The control group consisted of 15 healthy sheep of the same age group and characteristics. Blood samples were taken from the sheep in the patient groups twice, before the treatment and 1 week after the treatment. In the control group, blood samples were taken once.

Taken and Processing of Blood Samples

Blood samples were taken from the *Vena jugularis* using a holder and compatible sterile needle tip (Vacuette®, Greiner Bio-One GmbH, Austria) before and after treatment from sick sheeps and once from healthy sheep. For pre- and post-treatment hematological analysis from sheep, 2 mL blood samples were collected into the EDTA tube (BD Vakutainer®, BD, UK). Whole blood analysis was measured using by an automated whole blood analyzer (VG-MS4e®, Melet Schloesing, France) within half an hour. Five mL blood samples taken into vacuum gel serum tubes (BD Vakutainer®, BD, UK) were kept at room temperature for approximately 1 hour, and then centrifuged at 3000 rpm for 10 minutes (Hettich Rotina

380R®, Hettich, Germany), then serum samples were extracted and measurements were performed daily. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, glucose, urea, total protein, albumin, magnesium, and creatin kinase (CK) were measured by using a fully automated biochemistry machine (Mindray BS120®, Mindray Medical Technology Istanbul, Turkey).

Taken of Bronchoalveolar Lavage Fluid Samples

Before taking the bronchoalveolar lavage, both nostrils of the sheep were cleaned with alcohol cotton to prevent nasal contamination. After the head and neck extension of the sheep was achieved, a disposable sterile nasogastric tube (4 mm x 1210 mm, Bicakcilar, Istanbul) was advanced transnasalally through the trachea until it encountered a slight resistance. Whether the carina region was reached or not was followed up with a recurrent cough reflex (Ok et al., 2019, İder and Maden, 2019). When the carina was reached, the nasogastric tube was withdrawn 1-2 cm, 15 mL of sterile saline (37 ºC, 0.9% Isotonic Sodium Chloride-FTS) was infused into the trachea and immediately aspirated. Approximately 3-5 mL of the given fluid was withdrawn. BALf samples were sent to Kafkas University Veterinary Faculty Microbiology Department laboratory for bacterial analysis.

Microbiological Procedure

The samples of bronchoalveolar lavage fluid samples were centrifuged at 3000 rpm for 3 minutes and the supernatant was removed, the sediment was homogenized with 100 µL FTS and cultivated in blood agar medium supplemented with 7% sheep blood. At the end of 24-48 hours of incubation at 37ºC under aerobic conditions, colonies with a diameter of 1-2 mm, colony morphology, gray, smooth or mucoid and without hemolysis were passed into blood agar with 7% blood for further biochemical tests and incubated under the same conditions. In biochemical tests, colonies that are catalase, oxidase positive, immobile, indole positive, urease negative, *Mac Conkey non-growing were defined as P*. multocida (Bergey, 1994).

Treatment Management

Sick sheep were kept under surveillance in separate boxes during the treatment. A standard supportive treatment protocol including A, B, C, D and E vitamins were performed to the all diseased sheeps. For vitamin supplementation, the sheeps were given parenterally vitamin B complex (Berovit B12®, Ceva, Australia) in a practical dose of 8-10 mL/sheep for 7 days, vitamin C (Maxivit-C®, Bavette, Turkey) at a dose of 4-6 mg/kg for 3 days, and vitamin ADE at a single subcutaneous dose of 1 mL/50kg (Ademin®, Ceva, Australia). In addition to the standard treatment, enrofloxacin was administered at a dose of 5 mg/kg once a day for 1 week intramuscularly in group 1. In Group 2, a single dose of 2.5 mg/kg of tulathromycin was administered intramuscularly. No drug was applied to the healthy control group sheep.

Statistical Analysis

The normal distribution of the data of the groups before and after the treatment and the control group was evaluated using visual methods (histogram graph and Q-Q graph) and Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used for the multiple comparison of the pre-treatment and post-treatment groups (group 1 and group 2) and the control group, and Tukey HSD test was used for post hoc comparison. The data obtained before and after the treatment were compared with the Paired Sample t-Test. The data obtained in the study were reported as mean ± standard error (SEM). All analyzes were performed with the SPSS® software program (SPSS® Statistics 26.0, Chicago, IL, USA). Differences obtained

in group comparisons were considered significant at P≤0.05.

RESULTS

In our study, physical examination findings such as rectal temperature, respiratory rate and heart rate before treatment were statistically significant compared to the control (P<0.001, Table 1). Total leukocyte count was found to be higher in the patient groups before treatment compared to the control group (P=0.010, Table 1). The physical examination findings and other hematological parameters are given in Table 1. ALT, AST, ALP, urea and CK concentrations were found to be statistically significantly higher in the patient groups compared to the control group before treatment (P<0.05, Table 2). Among the other biochemical parameters presented in the study, GGT, total protein, total bilirubin, albumin, magnesium and glucose levels are given in Table 2 (P>0.05).

Table 1. Physical examination findings and hematology of sick and healthy sheep

Parameters	Groups	N	Before treatment	After treatment	P1 value
			Mean±SEM		
Rectal temperature (°C)	Group 1	15	39.98± 0.14^{B}	38.70±0.08	<0.001
	Group 2	15	39.05±0.21^{A}	38.89±0.13	<0.001
	Control	15	38.48±0.15^{A}		-
	P2 value		<0.001	0.092	-
Heart beats/min	Group 1	15	108.07±4.28^{B}	74.27±5.28	<0.001
	Group 2	15	105.47±8.41^{B}	71.73±2.63	<0.001
	Control	15	72.53±2.47^{A}		-
	P2 value		<0.001	0.885	-
Breaths/min	Group 1	15	38.40±1.22^{B}	26.80±1.66	<0.001
	Group 2	15	31.93±3.85^{AB}	31.47±2.86	0.923
	Control	15	24.53±1.33^{A}		-
	P2 value		<0.001	0.064	-
Total leukocytes count (×10^{3}/µL)	Group 1	15	14.46±2.58^{AB}	9.66±0.81	0.038
	Group 2	15	18.79±2.68^{B}	9.40±0.88	0.004
	Control	15	8.99±0.58^{A}		-
	P2 value		0.010	0.826	-
Lymphocytes count (x10^{3}/µL)	Group 1	15	7.11±2.09	5.21±0.56	0.394
	Group 2	15	10.17±2.50	5.28±0.65	0.077
	Control	15	5.85±0.48		-
	P2 value		0.269	0.686	-
Monocytes count (x10^{3}/µL)	Group 1	15	0.52±0.04	0.59±0.04	0.272
	Group 2	15	0.65±0.06	0.61±0.07	0.693
	Control	15	0.55±0.05		-
	P2 value		0.267	0.766	-
Granulocytes count (x10^{3}/µL)	Group 1	15	6.81±1.01^{B}	3.85±0.57	0.018
	Group 2	15	7.97±1.11^{B}	3.57±0.33	0.002
	Control	15	2.58±0.15^{A}		-
	P2 value		<0.001	0.072	-
Red blood cell count (x10^{6}/µL)	Group 1	15	13.21±0.85	13.69±0.46	0.628
	Group 2	15	13.93±1.39	13.05±0.55	0.564
	Control	15	12.17±0.42		-
	P2 value		0.448	0.098	-
Mean red cell volume (fL)	Group 1	15	37.14±1.51^{A}	38.22±0.93	0.550
	Group 2	15	36.35±0.90^{A}	39.68±1.18	0.211
	Control	15	42.64±2.03^{B}		-
	P2 value		0.002	0.107	-
Hematocrit (%)	Group 1	15	47.42±2.30	51.86±1.41	0.114
	Group 2	15	46.49±4.10	51.13±1.44	0.296

	Control	15	46.01±2.05		-
	P2 value		0.943	0.064	-
Hemoglobin (g/dL)	Group 1	15	12.54±0.63	11.57±0.35	0.189
	Group 2	15	12.28±0.52	11.80±0.33	0.451
	Control	15	11.16±0.20		-
	P2 value		0.117	0.332	-
Platelet count (x10^3/µL)	Group 1	15	305.40±51.05	473.40±40.50^{b}	0.016
	Group 2	15	352.33	349.87±25.78^{ab}	0.962
	Control	15	354±13^{a}		-
	P2 value		0.656	0.015	-

SEM: Standard error of mean. N: Number of calves in the groups. P<0.05: Statistically significant. P1: Expresses the statistical significance level within the group. P2: Expresses the statistical significance level between groups. A,B: Different letters in the same column indicate statistical difference between groups before treatment. a,b: Different letters in the same column indicate statistical difference between groups after treatment.

Table 2. Serum biochemical parameters of sick and healthy sheep

Parameters	Groups	N	Before treatment	After treatment	P1 value
			Mean±SEM		
Alanine aminotransferase (IU/L)	Group 1	15	71.22±6.05^{B}	78.53±9.13^{b}	0.509
	Group 2	15	66.96±5.52^{B}	59.48±5.24^{ab}	0.334
	Control	15	40.54±5.33^{Aa}		-
	P2 value		<0.001	0.001	-
Aspartate aminotransferase (IU/L)	Group 1	15	188.87±10.89^{B}	181.44±15.05	0.819
	Group 2	15	194.40±12.26^{B}	161.12±8.46	0.034
	Control	15	121.09±7.74^{A}		-
	P2 value		0.002	0.077	-
Gamma glutamyl transferase (IU/L)	Group 1	15	44.96±1.91	37.28±3.24	0.061
	Group 2	15	43.58±2.38	44.08±2.13	0.877
	Control	15	42.79±2.24		-
	P2 value		0.779	0.155	-
Alkaline phosphatase (IU/L)	Group 1	15	122.52±4.78^{B}	103.43±5.82^{ab}	0.081
	Group 2	15	133.77±11.99^{B}	128.16±7.04^{b}	0.877
	Control	15	75.06±6.34^{Aa}		-
	P2 value		<0.001	0.022	-
Urea (mg/dL)	Group 1	15	80.60±1.85^{B}	64.16±3.12	0.020
	Group 2	15	71.73±2.70^{B}	57.30±3.23	0.023
	Control	15	52.34±2.98^{A}		-
	P2 value		<0.001	0.281	-
Total bilirubin (mg/dL)	Group 1	15	0.020±0.01	0.010±0.008	0.559
	Group 2	15	0.030±0.01	0.010±0.009	0.699
	Control	15	0.04±0.01		-
	P2 value		0.089	0.205	-
Total protein (g/dL)	Group 1	15	6.87±0.36	7.36±0.47	0.063
	Group 2	15	7.33±0.43	7.86±0.31	0.128
	Control	15	7.16±0.22		-
	P2 value		0.231	0.111	-
Albumin (g/dL)	Group 1	15	3.46±0.10	3.53±0.15	0.719
	Group 2	15	3.31±0.31	3.36±0.23	0.907
	Control	15	3.36±0.12		-
	P2 value		0.867	0.731	-
Magnesium (mg/dL)	Group 1	15	3.32±0.27	2.79±0.12	0.088
	Group 2	15	3.10±0.11	2.84±0.15	0.189
	Control	15	3.29±0.18		-
	P2 value		0.717	0.064	-
Creatine kinase (IU/L)	Group 1	15	385.48±46.06^{B}	438.70±54.44^{b}	0.548
	Group 2	15	292.19±42.24^{AB}	352.59±29.51^{ab}	0.251
	Control	15	199.81±14.46^{Aa}		-

	P2 value		0.004	0.003	-
Glucose (mg/dL)	Group 1	15	128.27±19.19	111.53±15.45	0.503
	Group 2	15	94.27±14.53	96.27±8.07	0.905
	Control	15	80.53±12.02		-
	P2 value		0.094	0.213	-

SEM: Standard error of mean. N: Number of calves in the groups. P<0.05: Statistically significant. P1: Expresses the statistical significance level within the group. P2: Expresses the statistical significance level between groups. A,B: Different letters in the same column indicate statistical difference between groups before treatment. a,b: Different letters in the same column indicate statistical difference between groups after treatment.

DISCUSSION

Anorexia, fever, dyspnea, serous or mucopurulent nasolacrimal discharge, tachypnea, and tachycardia are among the clinical symptoms seen in respiratory system infection (Bulut, 2019). In our study, there were fever, anorexia, tachycardia and tachypnea findings in the sheep in the patient groups, which was consistent with the literature. Along with the treatments, physical examination findings in both group 1 and group 2 were similar to the control.

Leukocytosis is observed as a result of defense mechanisms in respiratory system diseases and bacterial infections (Akyüz & Gökce, 2021; Akyüz et al., 2022). In the study we presented, respiratory system infection caused by *P. multocida* was formed. Probably as a result of the developing bacterial infection, defense mechanisms were activated and it was determined that leukocytosis and granulocytosis were formed in the patient groups. The fact that total leukocyte and granulocyte counts were similar to the control after treatment in groups 1 and 2 showed that tulathromycin and enrofloxacin treatments were successful in controlling the infection. No statistically significant result was observed between the groups in other hematological parameters.

Alkaline phosphatase concentrations increase in conditions such as cholestasis, stress, bone tissue destruction, and disruption of circulation in the hepatobiliary system. ALT and AST concentrations are used to determine muscle breakdown and liver damage (Soltesova et al., 2015; Bozukluhan et al., 2021). Previous studies showed that in pneumonia, liver perfusion is impaired, causing structural and functional damage to the liver (Bozukluhan et al., 2021). In addition, inflammation caused by mediators released from cells such as monocytes and macrophages causes hepatocellular dysfunction (Civelek et al., 2007). In our study, ALT, AST and ALP concentrations were found to be higher in sheep in groups 1 and 2 before treatment compared to the control. It may be due to the deterioration of liver perfusion resulting from pneumonia and stress. After treatment, ALT, AST and ALP concentrations were observed to decrease more significantly, especially in group 2 compared to group 1. The reason for the decrease in AST and ALP concentrations in the patient groups after treatment may be the reduction of stress, control of inflammation and restoration of liver tissue perfusion with treatment.

Urea concentration increases in cases of high protein catabolism, kidney diseases, infections and anorexia (Gokce & Woldehiwet, 1999; Bozukluhan et al., 2021). In our study, urea concentration before treatment was higher in groups 1 and 2 compared to the control. This increase in urea concentration was probably due to impaired kidney function in association with inflammation. This increase may also occur due to high protein catabolism due to anorexia in pneumonia. After treatment, urea reached close to control levels. CK concentration increases in muscle tissue destruction (Aydın et al., 2018). In the presented study, muscle tissue damage caused by infection may have occurred and CK concentration may have increased as a result.

In pneumonia, especially the cranial lobes of the lungs are affected (Milli et al., 2001; Caswel & Williams, 2007; McGavin et al., 2007; Çiftçi et al., 2015). In accordance with the literature, it was determined that especially the cranial lobes were affected more in the lung auscultation performed in our study. Enrofloxacin is a fluoroquinolone antibiotic with a broad spectrum of antibacterial activity. It has been reported to be effective against *P. multocida* (Suckow et al 1996). In the present study, the clinical improvement of the sick sheep in group 1 after enrofloxacin treatment was found to be consistent with the statement of being active against *P. multocida* in the literature.

In comparison of tulathromycin, florfenicol and amoxicillin treatments in goats with pneumonia, the most effective antibacterial was reported as tulathromycin (Ghanem et al., 2015). In another study, it was determined that tulathromycin showed high activity against common bacterial pathogens that cause respiratory tract disease. It has been reported that the reason for this is related to the rapid absorption and high bioavailability of the drug (Zhou et al., 2017). In our study, the faster clinical recovery of sheep in group 2 may be due to the rapid absorption of tulathromycin in the lungs and its high bioavailability. In another study, it was determined that after a single dose of 2.5 mg/kg tulathromycin administration to sheep with respiratory system disease, improvement was observed on the 5th day (Champour and Taghipour, 2015). In our study, clinical improvement in sheep in group 2 was similarly observed from the 3th day, which was found to be compatible with the study.

CONCLUSION

Especially in the infections occurring on the basis of herd, the fastest recovery with the least drug application is desired. In our study, clinical improvement was observed from the 3th day in group 2 and from the 5th day in group 1. We conclude that the administration of a single dose of tulathromycin is more beneficial and practical in *P. multocida*-induced sheep pneumonia in terms of both clinically earlier recovery and a single administration.

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