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RESEARCH ARTICLE

Safety of an antiprotozoal drug combination in sheep

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Koyunlara kombine antiprotozoal ilaç kullanımının güvenilirliği

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Öz

Amaç: Bu çalışmanın amacı kan parazitlerine karşı kullanılan imidokarb, buparvaquon ve oksitetrasiklinin koyunlarda maksimum doz ve sürede kombine kullanımının olası yan etkilerini belirlemektir.

Gereç ve Yöntem: Araştırmada 10 adet koyuna imidokarb (2.4 mg/kg), buparvaquon (2.5 mg/kg) ve oksitetrasiklin (20 mg/kg) birlikte kas içi yolla 3 gün ara ile iki kez uygulandı. Kan örnekleri uygulama öncesi (0 kontrol) ve sonrası 0.5, 1, 2, 3, 4, 5 ve 6. günler alındı. Malondialdehid, 8-hidroksi-2-deoksiguanosin, troponin I ve kreatin kinaz-MB isoenzim düzeyleri ELISA okuyucusunda belirlenirken, kalp, karaciğer ve böbrek fonksiyon parametreleri otoanalizörde ölçüldü. Ayrıca kan gazları ve hemogram parametreleri ölçüldü.

Bulgular: Uygulama sonrası koyunlarda oksidatif stres belirlenmezken ($p>0.05$), laktat dehidrogenaz, aspartat aminotransferaz, alanin aminotransferaz, kan üre nitrojen ile glikoz düzeylerinde artışlar belirlendi ($p<0.05$). Alkalen fosfataz, akyuvar sayısı ve sodyum düzeylerinde düşmeler gözlenirken ($p<0.05$), hemoglobin, bikarbonat, potasyum, iyonize kalsiyum ve klor düzeylerinde istatistiki dalgalanmalar belirlendi ($p<0.05$).

Öneri: Koyunlara imidokarb, buparvaquon ve oksitetrasiklinin kombine uygulamasının ciddi oksidatif stres, kardiyotoksisite ve nefrotoksisiteye neden olmadığı, fakat bu kombinasyonun karaciğer fonksiyonu ile kan gazları ve hemogram parametrelerini etkileyebileceği ifade edilebilir. Ancak hasta hayvanlarda bu kombinasyonun kullanılmasında dikkatli olunmalıdır

Anahtar kelimeler: İmidokarb, buparvaquon, oksitetrasiklin, güvenilirlik, koyun

Abstract

Aim: The aim of this study was to determine the possible side effects in sheep of combined administration of imidocarb, buparvaquone, and oxytetracycline, which are antiprotozoal drugs against blood-borne parasites, at the maximum dose and treatment period. .

Materials and Methods: Imidocarb (2.4 mg/kg), buparvaquone (2.5 mg/kg), and oxytetracycline (20 mg/kg) were administered simultaneously by intramuscular injection to 10 sheep, and a second combined dose was administered 3 days later. Blood samples were taken before (0 control) and at 0.5, 1, 2, 3, 4, 5, and 6 days after drug administrations. Malondialdehyde, 8-hydroxy-2′-deoxyguanosine, troponin I, and creatine kinase-MB isoenzyme levels were determined with ELISA reader, and cardiac, hepatic, and renal damage markers were measured with autoanalyzer. Blood gas and hemogram parameters were also determined.

Results: No oxidative stress ($p>0.05$) was observed in the sheep, whereas increased ($p<0.05$) lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and glucose levels were determined. Although decreased ($p<0.05$) alkaline phosphatase, white blood cell counts, and sodium levels were measured, statistically significantly fluctuations were observed ($p<0.05$) in hemoglobin, bicarbonate, potassium, ionized calcium, and chlorine levels.

Conclusion: The combination of imidocarb, buparvaquone, and oxytetracycline have not cause serious oxidative damage, cardiotoxicity, and nephrotoxicity in sheep, but this combination may show transient effects on liver function and blood gas and hemogram values. Therefore, caution should be exercised when using this combination in infected sheep.

Keywords: Imidocarb, buparvaquone, oxytetracycline, safety, sheep

Introduction

Diseases transmitted by ticks can cause serious problems in the world, and raising awareness about tick control has started to gather pace. The World Health Organization (WHO) declared 2015 the year of vector-borne diseases (Inci et al 2016a). Many zoonotic diseases are transmitted by arthropods (Inci and Duzlu 2009), and ticks can spread more than one disease at the same time (Nuhoglu et al 2008).

Babesiosis is caused by *Babesia* species, which are transmitted by ticks and infect red blood cells in domestic and wild animals, and humans (Baneth 2018). Hyperthermia, loss of appetite, depression, hemoglobinemia, hemoglobinuria, icterus, abortion, nervous or respiratory symptoms, and death may occur in infected animals (Jabbar et al 2015). Imidocarb dipropionate is the antiprotozoal drug used to treat babesiosis (Yazar 2018a). Although its mechanism of action is still not fully understood, it is thought that the drug may inhibit the entry of inositol into infected red blood cells or alter polyamine metabolism (Wise et al 2013). Cholinergic effects, pain during injection, hypersalivation, drooling, nasal drip, panting, restlessness, diarrhea, renal tubular necrosis, and hepatic necrosis may occur as side effects in animals after imidocarb dipropionate injection (Baneth 2018, Yazar 2018b). Hence, therapeutic dosage calculation for imidocarb dipropionate should be performed with caution because of its toxicity (Gazyagci and Aydenizoz 2010, Yazar 2018b). In general, drug-mediated side effects are commonly associated with the dosage regimen. An imidocarb dipropionate dose of 1.2 mg/kg is accepted as safe, whereas 2.4 and 4.8 mg/kg doses may cause temporary or mild toxicity in sheep (McHardy et al 1986).

Theileriosis is caused by intracellular protozoan parasites of the genus *Theileria,* which are transmitted by ticks. *Theileria* species infect primarily cattle, goats, and sheep. Hyperthermia, enlarged lymph nodes, tachycardia, nasal discharge, weakening, reduction of condition, pulmonary distress, and death may be observed in infected animals (Jabbar et al 2015). Buparvaquone is used to treat theileriosis (Yazar 2018b), and acts by inhibiting the respiratory system of parasites (Ghauri et al 2019). Although it is not approved for use in sheep, it can be administered extra-label for treating sheep theileriosis (El-Hussein et al 1993, Zia-Ur-Rehman 2010, Hasheminasab et al 2018). However, studies on the safety of buparvaquone in sheep are limited (Isik et al 2018).

Anaplasmosis is a tick-transmitted rickettsial infection caused by *Anaplasma* species in the ruminants. Hyperthermia, icterus, anemia, anorexia, depression, abortion, and death may occur in infected animals (Jabbar et al 2015). Oxytetracycline or imidocarb dipropionate is used in its treatment (Yazar 2018a). Oxytetracycline may cause local reactions at the injection site and photosensitization as side effects. The main mechanism of action of tetracyclines is inhibition of bacterial protein synthesis. However, other mechanisms have also been reported (Yazar 2018b).

Although the side effects of imidocarb (Baneth 2018, Yazar 2018b), buparvaquone (Isik et al 2018), and oxytetracycline (Yazar 2018b) have been studied separately in sheep, they have not been studied for the combination of these three drugs. It has been hypothesized that these drugs may cause undesirable effects when used together at maximum dose and duration. These side effects may be determined by measuring parameters of oxidative status, organ (heart, liver, and kidney) damage, hemogram, and blood gas.

The aim of this research was to determine the effects of combined usage of the three antiprotozoal drugs, imidocarb, buparvaquone, and oxytetracycline, on oxidative status markers (malondialdehyde [MDA], 8-hydroxy-2′-deoxyguanosine [8-OHdG]), cardiac damage (troponin I, creatine kinase-MB [CK-MB] isoenzyme, lactate dehydrogenase [LDH], and aspartate aminotransferase [AST]), hepatic damage (alkaline phosphatase [ALP], alanine aminotransferase [ALT], AST, gamma-glutamyltransferase [GGT], and total protein), renal damage (blood urea nitrogen [BUN] and creatinine) markers, and hemogram (white blood cell [WBC], red blood cell [RBC], platelet, hemoglobin, and hematocrit), and blood gas (pH, pCO_2, pO_2, sO_2, base(ecf), HCO_3-, potassium, sodium, ionized calcium, chlorine, glucose, and lactate) values.

Material and Methods

Animals and ethics approval

Ten merino sheep (aged 15–18 months, mean weight 59.90 ± 2.2 kg) were used in this study. Study protocol was approved by Ethic Committee of Veterinary Faculty (2019-22).

Drug applications and sample collections

Imidocarb dipropionate (2.4 mg/kg, Imocel Inj., Sol., CLK-Pharma Ilac San., Ankara, Turkey), buparvaquone (2.5 mg/kg, Parvakuvil Inj., Sol, Vilsan, Istanbul, Turkey), and oxytetracycline (20 mg/kg, Primamycin LA Inj, Zoetis, Istanbul, Turkey) were simultaneously administered through intramuscular injection into the animals and the injections were repeated after a 3-day interval. Blood samples were taken before injection (0 control) and at 0.5, 1, 2, 3, 4, 5, and 6 days after administration of the drugs.

Oxidative stress, organ damage, hemogram and blood gases values

MDA (Bioxytech MDA-586 kit, OXISResearch, Portland, OR,

USA), 8-OHdG (sheep 8-hydroxy-2′-deoxyguanosine; Bioassay Technology Laboratory, Shanghai, China), troponin I (sheep troponin I ELISA kit, Bioassay Technology Laboratory), and CK-MB isoenzyme (sheep creatine kinase-MB isoenzyme, Bioassay Technology Laboratory) were measured with an ELISA reader (MWGt Lambda Scan 200, Bio-Tec Instruments, Winooski, VT, USA). Serum levels of LDH, AST, ALP, ALT, GGT, total protein, BUN, and creatinine were measured with an auto-analyzer (BT-300 plus, Roma, Italy), while hemogram and blood gas values were determined with a hemocell counter (MS4E Hematology Cell Counter, Mellet Schloesing Laboratories, France) and blood gas analyzer (ABL90 Flex Analyzer, Denmark), respectively.

Data analysis

Results are presented as mean ± standard error. The differences in the measured parameters between the blood samples collected at different times after drug administration were analyzed with ANOVA and the post hoc Tukey's test (SPSS 22.0). $p<0.05$ level was accepted as statistically significant.

Results

Oxidative stress and organ damage markers

The effects of the drug combination on MDA, 8-OHdG, and markers of organ damage are shown in Table 1. No statistically significant differences ($p>0.05$) were detected between blood samples collected at different times after drug administration for oxidative status (MDA and 8-OHdG) and the main cardiac damage markers (troponin I and CK-MB isoenzyme). Combined drug administration increased ($p<0.05$) LDH levels within one day after treatment. Elevated AST levels ($p<0.05$) were observed in the last 3 days, while decreased ALP levels ($p<0.05$) were seen in the last 2 days. In addition, significant transient increases in BUN and glucose levels were observed ($p<0.05$).

Hemogram and blood gas parameters

The effects of the drug combination on hemogram and venous blood gas parameters are shown in Table 2. Decreased WBC levels ($p<0.05$) were determined after the second set of injections, and decreased sodium levels ($p<0.05$) were measured at the final sampling day. In addition, statistically significant fluctuations ($p<0.05$) were observed in the levels of hemoglobin, bicarbonate, potassium, ionized calcium, and chlorine. No clinical abnormalities were observed during the experimental period.

Discussion

The tick-borne diseases (Babesiosis, theileriosis, and anaplasmosis) are important in the world (Inci et al 2016b). Although drugs are available to treat these diseases, when multiple diseases are observed together, drug combinations may be required (Yazar 2018a). Mixed babesiosis, theileriosis, and anaplasmosis infection has been reported in animals (Javed et al 2014). This may lead to increased risk of side effects due to multiple drug usage.

In this study, imidocarb, buparvaquone, and oxytetracycline were administered together to sheep at maximum dose

Table 1. Effects of antiprotozoal drug combination (Imidocarb dipropionate 2.4 mg/kg, IM + buparvaquone 2.5 mg/kg, IM + oxytetracycline 20 mg/kg, IM, 2 times with 3 days interval) on lipid peroxidation, systemic oxidative stress, cardiac, hepatic and renal damage markers (mean ± SE)d convertion ratio of quail breeders

Parameters	0. day	0.5 day	1. day	2. days	3. days	4. days	5. days	6. days
MDA ng/mL	0.50±0.17	0.25±0.07	0.54±0.30	0.29±0.11	0.25±0.06	0.74±0.30	0.42±0.24	0.26±0.08
8-OHdG ng/mL	16.77±4.53	16.26±3.83	15.56±3.04	17.64±4.74	13.18±2.50	15.40±3.02	13.59±3.51	8.59±1.39
Trop I ng/L	174.12±39.94	140.77±46.17	162.20±45.44	170.43±27.62	156.04±58.20	182.34±28.89	134.36±21.61	127.44±14.99
CK-MBiso ng/mL	4.34±1.18	3.55±0.73	4.63±1.24	3.72±0.73	3.52±0.67	2.96±0.35	4.25±0.70	4.25±0.70
LDH U/L	1181.90±66.70^{b}	1812.10±113.70^{a}	1709.50±176.15^{a}	1383.30±136.29^{ab}	1343.90±97.43^{ab}	1708.70±129.77^{a}	1307.30±80.53^{ab}	1347.40±79.28^{ab}
AST U/L	98.10±2.77^{c}	165.00±9.00^{b}	183.90±11.26^{b}	162.30±11.51^{b}	146.60±9.87^{bc}	237.80±19.84^{a}	186.50±13.35^{ab}	168.50±9.99^{b}
ALT U/L	29.20±1.53^{c}	35.70±1.77^{bc}	37.40±1.86^{bc}	36.70±2.84^{bc}	35.90±2.45^{bc}	49.60±3.91^{a}	44.20±2.92^{ab}	42.70±2.54^{ab}
ALP U/L	181.40±8.83^{a}	182.70±9.29^{a}	162.30±7.77^{ab}	151.70±8.91^{ab}	149.00±8.28^{ab}	144.10±12.20^{ab}	128.50±8.45^{b}	135.60±8.91^{b}
GGT U/L	60.50±2.48	60.30±1.46	59.60±0.88	57.60±1.02	59.90±1.22	60.20±1.38	58.60±1.12	62.70±2.67
Tprot g/dL	7.45±0.15	7.27±0.19	7.20±0.14	6.82±0.25	7.02±0.16	6.94±0.15	6.77±0.14	7.03±0.11
BUN mg/dL	10.90±0.43^{b}	10.50±0.54^{b}	14.00±0.51^{a}	11.70±0.49^{b}	10.60±0.45^{b}	11.70±0.44^{b}	12.50±0.37^{ab}	11.60±0.56^{b}
Creat mg/dL	1.35±0.05	1.57±0.08	1.51±0.08	1.32±0.06	1.37±0.07	1.60±0.08	1.42±0.08	1.39±0.06
Glucose mg/dL	67.50±1.94^{bc}	65.60±1.20^{c}	69.90±2.06^{bc}	69.40±1.11^{bc}	74.60±1.60^{ab}	78.20±2.13^{a}	69.20±1.20^{bc}	66.00±1.29^{c}
Lactate mmol/L	3.36±0.77	3.76±1.30	1.45±0.19	2.09±0.25	3.39±0.42	3.57±0.45	3.12±0.71	3.96±0.54

a, b, c: Different letters in the same line are statistically significant (P<0.05, tukey test). MDA: Malondialdehyde, 8-OHdG: 8-hydroxy-2-deoxyguanosine, Trop I: Troponin I, CK-MBiso: Creatine kinase-MB isoenzyme, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, Tprot: Total protein, BUN: Blood urea nitrogen, Creat: Creatinine.

Table 2. Effects of antiprotozoal drug combination (Imidocarb dipropionate 2.4 mg/kg, IM + buparvaquone 2.5 mg/kg, IM + oxytetracycline 20 mg/kg, IM, 2 times with 3 days interval) on hemogram and venous blood gas parameters (mean ± SE)

Parameters	0. day	0.5 day	1. day	2. days	3. days	4. days	5. days	6. days
WBC 10^9/L	8.17±1.33^{a}	6.87±0.43^{ab}	6.45±0.46^{ab}	6.25±0.55^{ab}	5.10±0.47^{ab}	4.40±0.94^{b}	6.80±0.64^{ab}	6.02±0.64^{ab}
RBC 10^{12}/L	14.17±0.47	14.09±0.59	13.17±0.32	12.78±0.40	12.91±0.35	13.26±0.53	13.16±0.53	14.05±0.36
Platelet 10^9/L	339.00±29.04	396.30±56.12	446.60±72.64	285.50±21.63	311.70±29.92	452.10±101.76	304.30±31.39	333.80±27.06
Hgb g/dL	12.54±0.41^{ab}	12.73±0.50^{a}	11.31±0.26^{ab}	11.13±0.26^{ab}	10.91±0.40^{b}	11.71±0.34^{ab}	11.66±0.47^{ab}	12.00±0.29^{ab}
Htc %	41.19±1.32	40.39±1.50	37.75±0.98	36.79±1.20	37.65±1.59	43.34±2.62	37.30±1.93	40.01±1.41
pH	7.41±0.01	7.40±0.20	7.44±0.01	7.45±0.01	7.42±0.01	7.42±0.01	7.44±0.01	7.42±0.01
pCO_2 mmHg	36.21±0.66	35.88±1.15	33.58±1.07	37.28±1.39	37.13±1.60	37.91±1.17	38.08±0.89	37.99±1.23
pO_2 mmHg	41.37±2.60	42.71±2.18	46.10±3.12	44.41±3.29	46.28±3.30	39.05±2.17	42.20±2.32	42.73±2.40
sO_2 %	60.81±4.61	62.71±3.25	66.13±2.81	64.74±5.71	66.81±5.09	56.92±4.33	55.53±6.14	62.07±4.05
Base(ecf) mmol/L	-0.88±1.22	-1.67±1.38	-0.73±0.60	1.83±0.69	0.02±0.68	0.33±0.80	2.05±0.69	0.51±0.79
HCO_3- mmol/L	23.33±0.89^{ab}	22.76±1.01^{b}	23.67±0.46^{ab}	25.50±0.54^{ab}	24.07±0.55^{ab}	24.10±0.58^{ab}	28.64±2.94^{a}	24.35±0.56^{ab}
K mmol/L	3.97±0.04^{ab}	4.17±0.12^{ab}	3.80±0.08^{b}	4.10±0.08^{ab}	4.12±0.08^{ab}	4.14±0.10^{ab}	4.08±0.09^{ab}	4.31±0.05^{a}
Na mmol/L	154.40±0.71^{a}	153.10±0.82^{abc}	153.80±0.94^{ab}	152.20±0.67^{abcd}	151.60±0.30^{bcd}	150.20±0.32^{d}	152.00±0.47^{abcd}	150.90±0.34^{cd}
iCa mmol/L	0.92±0.04^{bc}	1.00±0.03^{abc}	0.88±0.05^{c}	1.02±0.01^{a}	1.05±0.19^{a}	1.13±0.02^{a}	1.07±0.22^{a}	1.11±0.01^{a}
Cl mmol/L	110.80±0.77^{abc}	112.90±0.64^{a}	112.20±0.71^{ab}	110.20±0.71^{abc}	110.20±0.85^{abc}	110.30±0.53^{ab}	108.80±0.53^{c}	109.80±0.66^{bc}

a,b,c,d: Different letters in the same line are statistically significant (P<0.05, tukey test). WBC: White blood cell, RBC: Red blood cell, Plat: Platelet, Hgb: Hemoglobin, Htc: Hematocrit, pCO2: Partial pressure of carbon dioxide, pO2: Partial pressure of oxygen, sO2: Oxygen saturation, Base(ecf): Base excess extracellular fluid, HCO3-: Bicarbonate, K: Potassium, Na: Sodium, iCa: Ionized calcium, Cl: Chlorine.

and duration. The administration of the antiprotozoal drug combination did not affect (p>0.05) the levels of MDA, the lipid peroxidation marker (Ayala et al 2014) and 8-OHdG, the total systemic oxidative stress marker (Di Minno et al 2016) (Table 1). Although there is no information in the literature about the effects of imidocarb, buparvaquone, and oxytetracycline on blood 8-OHdG levels in sheep, imidocarb and buparvaquone are reported to have no effect on the levels of MDA in these animals (Ekici and Isik 2012, Isik et al 2018). In addition, the effects of tetracyclines on oxidative status are contradictory. Some studies have reported that tetracyclines exhibit antioxidant activity (Topsakal et al 2003, Clemens et al 2018), while others have reported that they cause oxidative stress (Gnanasoundari and Pari 2006, Yonar 2012). The results of this study suggest that imidocarb, buparvaquone, and oxytetracycline used in combination do not cause oxidative stress in sheep.

In this study, the administration of antiprotozoal drugs in combination did not affect (p>0.05) the levels of specific cardiac damage markers (troponin I and CK-MB isoenzyme), while they increased (p<0.05) the levels of nonspecific cardiac damage markers (LDH and AST), at 0.5 and 4 days. Although the LDH level decreased to the control level at the end of the experiment, the AST level remained high (Table 1). After treatment with imidocarb or buparvaquone, although increased levels of troponin I, CK-MB, and LDH have been reported for sheep (Ekici and Isik 2012, Ulusan et al 2016, Isik et al 2018) and increased AST levels for horses (Adams 1981), troponin I, LDH, and AST levels have been reported as unchanged in sheep (Ekici and Isik 2011, Isik et al 2018). In addition, doxycycline increased serum troponin I levels in calves (Karapinar et al 2019). These results suggest that combined usage of imidocarb, buparvaquone, and oxytetracycline may not cause serious cardiotoxicity in sheep because they do not have effects on specific cardiac damage markers.

Hepatic damage is assessed by measuring the levels of ALP, AST, ALT, GGT, and total protein. In this study, ALT and AST levels increased (p<0.05), whereas the ALP level decreased (p<0.05), and levels of other indicators (GGT, total protein) for hepatic damage were unchanged (p>0.05; Table 1). No changes have been reported in markers for hepatic damage (ALP, ALT, AST, GGT, total protein) in sheep after imidocarb or buparvaquone treatment (Ekici and Isik 2011, Ekici and Isik 2012, Isık et al 2018). However, imidocarb may cause hepatic necrosis (Baneth 2018), and increases the levels of ALT and AST in dogs (EMA 2019); it also increases the level of AST in horses (Adams 1981). The results of this study suggest that combined usage of imidocarb, buparvaquone, and oxytetracycline may cause slight hepatotoxicity in sheep.

A temporary increase in BUN levels was determined one day after administration of the three antiprotozoal drugs in combination in this study (Table 1). Although imidocarb or buparvaquone caused increases in BUN and creatinine levels in lambs (Ekici and Isik 2012, Isik et al 2018), renal tubular necrosis in dogs (Baneth 2018), and BUN levels in horses (Adams 1981) and cattle (Adams et al 1980), no changes have been reported in renal damage markers (BUN and creatinine) in lambs after imidocarb administration (Ekici and Isik 2011). Given that the increase in BUN levels in this study was minor and temporary, combined usage of imidocarb, buparvaquone, and oxytetracycline may be accepted as safe for the kidneys of sheep.

Administration of the three antiprotozoal drugs in combination caused a temporary increase in glucose levels at 4 days in this study (Table 1). However, other studies have not found any changes in glucose levels in sheep after imidocarb treatment (Ekici and Isik 2011, Ekici and Isik 2012). As the rise in glucose levels was slight and transient in this study, the effects of combined usage of imidocarb, buparvaquone, and oxytetracycline on glucose levels may be disregarded for sheep.

In the current study, application of antiprotozoal drugs in combination caused decreases ($p<0.05$) in the levels of WBC and sodium, and caused statistically significant fluctuations in other some hemogram and blood gas values (Table 2) Although slight changes in hemogram and blood gas values caused by imidocarb have been reported (Ekici and Isik 2011, Ekici and Isik 2012), no changes have been reported for hemogram values after buparvaquone treatment in sheep (Isik et al 2018). Therefore, combined usage of imidocarb, buparvaquone, and oxytetracycline may not have serious effects on hemogram and blood gas values.

Conclusion

In summary, simultaneous intramuscular injection of imidocarb (2.4 mg/kg), buparvaquone (2.5 mg/kg), and oxytetracycline (20 mg/kg) twice at an interval of 3 days has no effect on oxidative status, and does not cause serious cardiac, hepatic, or renal damage in healthy sheep. In addition, this combination does not cause serious changes in hemogram and blood gas values. However, the results may not be the same for infected sheep because of compromised health.

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Conflict of Interest

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