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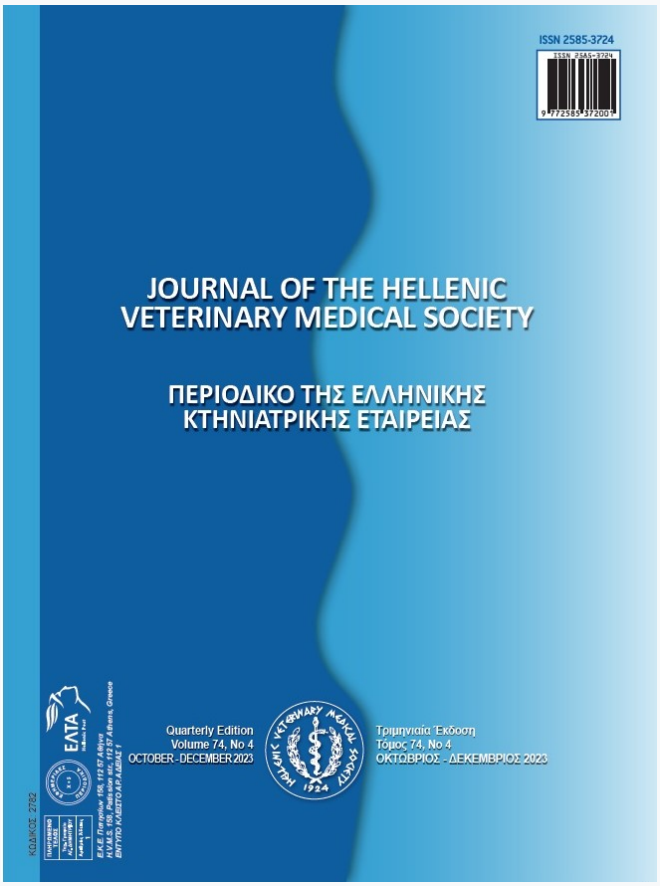

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Research article
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Evaluation of the effects of amiodarone and amiodarone+dobutamine on survival in tilmicosin-induced toxicity by electrocardiography and biochemical parameters in goats

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ABSTRACT: Tilmicosin shows different degrees of cardiotoxic effect in various animal species depending on the route of administration and dose. We aimed to determine the effects of amiodarone and amiodarone+dobutamine treatments on tilmicosincardiotoxicity and survival time. 18 healthy goats were divided into tilmicosin, tilmicosin+amiodarone and tilmicosin+amiodarone+dobutamine groups. After drug administrations, the survival times of the animals in all groups were recorded. In addition, blood was drawn from the animals just before they died. Haemogram, troponin I, CK-MB, and other biochemical parameters were measured in all blood samples. Prolonged survival was observed in the treatment groups compared to the tilmicosin group. In the treatment groups, decreases in haemogram parameters, albumin, and total protein levels caused by tilmicosin could not be prevented, while the increase in troponin I level was prevented. In conclusion, while cardiotoxicity due to high troponin from tilmicosin was prevented, the survival rate was not affected in both treatment groups, and the survival time was extended at differing rates. In case of accidental or deliberate overdose of tilmicosin in animals, in addition to the use of amiodarone+dobutamine, the survival time may be prolonged, and the success may increase if the necessary symptomatic treatments and equipment support are available.

***Keywords*:** Tilmicosin; Amiodarone; Dobutamine; Cardiotoxicity; Survival time

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INTRODUCTION

Amiodarone, which is an antiarrhythmic drug, was first developed as an antianginal in 1960s (Vassallo and Trohman, 2007). Although the exact mechanism of action of amiodarone is not known, it is stated that the drug has many effects, such as antiarrhythmic, vagotonic, sympatholytic, and negative chronotropic effects. Increased vagal activity has been reported to be significant 20th minutes. It also reduces Na^+/K^+-ATPase activity (Perkins et al., 1989; Kodama., 1997; Dias da Silva et al., 2002). Furthermore, amiodarone, which prolongs myocardial repolarization, can prolong the QT interval when combined with macrolide antibiotics (Vassalloand Trohman, 2007). Inotropes (dopamine, dobutamine, levosimendan, milrinone) increase cardiac contractility and improve renal perfusion. Therefore, inotropic therapy may be beneficial in patients with severely reduced cardiac output, systemic hypoperfusion, and end-organ dysfunction. Dobutamine, a sympathomimetic amine first developed in 1975, is used to increase cardiac contractility (GinwallaandTofovic, 2018).

Tilmicosin is a macrolide antibiotic. It acts by inhibiting protein synthesis and mainly shows activity against gram (+) aerobic bacteria. Tilmicosin is widely used in veterinary clinics, especially in respiratory system infections. This drug is not recommended for use in horses and goats due to its adverse effects. Depending on the dose and route of administration, the drug causes undesirable side effects such as diarrhea, cardiotoxicity, and death in laboratory and domestic animals. In addition, the drug was reported to cause death in humans due to accidental use (Jordan et al., 1993; Giguère et al., 2013; Diaz, 2014; Papich, 2016). Tilmicosin has serious side effects on the cardiovascular system. Its negative effect on the heart is determined by clinical findings, increased creatine kinase (CK) level, biochemical changes, and autopsy findings (Main et al., 1996; Yazar et al., 2001; Yapar et al., 2006; Christodoulopoulos, 2009). Positive chronotropy and negative inotropy are observed in high doses of tilmicosin toxicity, and it also shortens the QT interval (Jordan et al., 1993; CVMP, 2009). Although the exact cardiotoxic effect mechanism of tilmicosin is unknown, it is argued that it may be due to the blocking of Ca^{++} channels (Lust et al., 2011). Although there is no experimental study on tilmicosincardiotoxicity in goats, there are two articles and one case report about its pharmacokinetics and effect on the immune system (Ramadan, 1997; Coskun et al., 2012; El Sayed, 2016). It has been reported that approximately 1 minute after tilmicosin (15 mg/kg, SC) injection in a lamb (15 days, 6.08 kg), lying on the sternum, mild respiratory distress and subsequent central nervous system (CNS) depression were observed. An increase in heart rate was also detected. It has been reported that the lamb died approximately 15 minutes later and there were multiple ventricular septal defects in the heart in its necropsy (Christodoulopoulos, 2009). Previous studies show that the cardiotoxic effect of tilmicosin may be associated with oxidative damage in the heart (Yazar et al., 2002; Elazab et al., 2014). After intravenous administration of tilmicosin at doses of 0.25, 1, 2.5 and 5 mg/kg in dogs, heart rate increased in a dose-dependent manner. It has been reported that this situation is not the result of beta receptor stimulation. The negative inotropic effect can be corrected with intravenous dobutamine or dopamine. In addition, isotonic fluid may be given for hypotension. Beta-blockers, epinephrine and norepinephrine are not used (Main et al., 1996; Lust et al., 2011). Use of beta-blockers such as propranolol worsens cardiac effects. In addition, there is no specific antidote used for tilmicosin cardiotoxicity (Diaz, 2014; Main et al., 1996). When intravenous exposure to tilmicosin occurs, intravenous calcium administrations can reverse the cardiovascular effects (Lust et al., 2011).

Amiodarone is successfully used in AV tachycardia because it causes a decrease in heart rate after intravenous administration (VassalloandTrohman, 2007). In a clinical study, it is reported that the use of intravenous amiodarone reduces sudden deaths after acute myocardial infarction (Heidenreich et al., 2002). In addition, amiodarone has a B1-adrenoreceptor blocking effect (Bacq et al., 1976). In a study, it was reported that all 10 rats died within 10 hours after a single dose of tilmicosin (360 mg/kg, subcutaneous) was administered. In the same study, amiodarone (25 mg/kg, intravenous) was administered 8 minutes after a single dose of tilmicosin (360 mg/kg, subcutaneous) was administered to 10 rats; 2 of the rats died at the 2nd hour and 4 at the 12th hour, and the remaining 4 rats survived (Er et al., 2014). It has been reported that administration of tilmicosin in dogs inhibits transmembrane calcium flux and causes a negative inotropic effect. This effect has been improved by dobutamine, which has a positive inotropic effect (Main et al., 1996).

In the research, it was hypothesized that a treatment protocol can be developed that can be used in

macrolide group antibacterial drug toxicity, which has serious cardiotoxic effects in humans and animals. To investigate this, goats were used in the experimental study to test tilmicosin. Goats are known to be the most sensitive species to this drug, which is commonly used for treating respiratory tract infections in cattle and sheep (Christodoulopoulos et al., 2002; Papich, 2016). The aim of this study is to determine the effects of the amiodarone and amiodarone+dobutamine treatments on ECG, haemogram and biochemistry in tilmicosin cardiotoxicity. In addition, the study is the first experimental study for the treatment of tilmicosin toxicity in goats.

MATERIALS AND METHODS

Animals and Approval by the Ethics Committee

A total of 18 female goats (6-7 months old, 16-21 kg) were used in the study, and the procedure was approved by the Ethics Committee of Experimental Medical Practice and Research Center of Animal Experiments of Selcuk University, Konya, Turkey (2017-09). All procedures using animals complied with the Ethical Principles in Animal Research.

Animal preparation and experiment protocol

The animals were given 1 week to adapt to the environment. At the end of this period, the animals were divided into 3 groups (Tilmicosin, Tilmicosin+Amiodarone and Tilmicosin+Amiodarone+Dobutamine) with 6 animals in each group. For the measurement and comparison of haemogram and biochemical parameters, blood was drawn from the vena jugularis of the animals before tilmicosin administration and before death in agonic state. In all treatment groups, ECG imaging was initiated prior to administration of tilmicosin to monitor abnormal cardiac electrical behaviour in the heart and to detect change in QT interval and continued as long as the animal survived. A bipolar base apex lead electrogram (Compact 7, Medical Econet, Germany) was performed when the animals were determined to be in a quiet standing position (without sedation and with minimal restraint) using an alligator-type electrode attached to the skin, and the electrocardiography traces were recorded (paper speed: 25 millimeters second [mm/s]; calibration at 1 millivolt [mV]=1 centimeter [cm]). The positive electrode of lead I (left arm) was attached to the skin of the fifth intercostals space just caudal to the olecranon, and the negative electrode (right arm) was attached to the jugular furrow on the lower 1/3 of the left side of the neck, and the earth electrode was attached to the withers. Alligator clips were affixed to the skin after application of methyl alcohol. Tilmicosin (Micotil 300, Elanco) was administered intramuscularly at a dose of 50 mg/kg in all animals in all groups. The dose of tilmicosin was determined by evaluating previous studies on goats (Ramadan, 1997; El Sayed et al., 2016). A cannula was inserted into the ear vein of animals in the tilmicosin+amiodarone group, and amiodarone (Cordarone 150 mg IV, Sanofi-Aventis) 3 mg/kg bolus was administered through the ear vein 1 minute after tilmicosin administration along with an infusion of 3 mg/kg/minute from the 5th minute. Cannulas were inserted into both ear veins of the animals in the tilmicosin+amiodarone+dobutamine group, and amiodarone (3 mg/kg) was administered through the ear vein as a bolus 1 minute after tilmicosin administration. Two minutes after tilmicosin administration, dobutamine (MEKARD 250 mg/20 ml, Polifarma) was administered as an infusion of 7.5 microgram/kg/minute in the other ear vein. Administration of amiodarone as an infusion through the ear vein was started 5 minutes after tilmicosin administration.

Laboratorial analysis

Since death was reported in the first 15 minutes in lambs in a previous study, each animal was carefully monitored for the first 15 minutes in the current study. The time of death of all animals was recorded. Troponin I (Goat Troponin I ELISA kit, Bioassay Technology Laboratory, Shanghai, China) and CK-MB (Goat CK-MB ELISA kit, Bioassay Technology Laboratory, Shanghai, China) levels in the ELISA reader (MWGt Lambda Scan 200, Bio-Tek Instruments, Winooski, VT, USA) and albumin, total protein, AST, ALT, triglyceride, cholesterol, urea and creatinine levels in the autoanalyzer (BT-300 plus, Rome, Italy) were measured.

Statistical analysis

Statistical analysis of survival time data from results was performed using SPSS 25.0 (SPSS, Inc., USA) software. While parametric data such as biochemical and haemogram values were evaluated with the T-test, survival time was evaluated with the Kruskal-Wallis and post hoc Dunn-Bonferoni test, which is a non-parametric test. All values were presented as mean±standart error. $P \leq 0.05$ was considered statistically significant.

RESULTS

ECG and survival times

In the current study, ECG and survival times of animals in each group were recorded following drug administration. While tilmicosin administration caused a shortening in the QT interval, both treatment groups counteracted this shortening. ECG images of 2 animals from each group are presented in Figure 1. While survival time was 55.6 minutes in animals in the tilmicosin group, it was recorded as 81.6 and 192 minutes in the tilmicosin+amiodarone and tilmicosin+amiodarone+dobutamine groups, respectively. Although this time was prolonged in both treatment groups, there was a statistical difference in the tilmicosin+amiodarone+dobutamine group ($P<0.05$, Table 1).

Figure1. ECG images of Tilmicosin (T), Tilmicosin+Amiodarone (T+A), Tilmicosin+Amiodarone+Dobutamine (T+A+D).

Biochemical

Animals in the tilmicosin group died within 1 hour. In the blood samples taken just before death, increases in troponin I, triglyceride and creatinine levels (P≤0.05), and decreases in WBC, RBC, haemoglobin, haematocrit, albumin and total protein values (P≤0.05) were recorded. A statistically insignificant increase in CK-MB was observed (P>0.05, Table 2). An approximately 1.5-fold increase in survival was observed as a result of the use of amiodarone. During this prolonged period, WBC, RBC, haemoglobin, haematocrit, albumin, total protein and cholesterol levels decreased (P≤0.05) and CK-MB, triglyceride and creatinine levels increased (P≤0.05). The increase in troponin I level, which indicates cardiotoxicity caused by tilmicosin, was prevented in this treatment group (Table 3). In the tilmicosin+amiodarone+dobutamine group, a significant prolongation in survival was detected (approximately 3.5 times). However, decreases were determined in WBC, RBC, haemoglobin, haematocrit, albumin, total protein and cholesterol levels (P≤0.05). Increases in troponin I, CK-MB and creatinine levels caused by tilmicosin were prevented in this treatment group (Table 4).

Table 1. Survival times (mean±SE) in the tilmicosin, tilmicosin+amiodarone and tilmicosin+amiodarone +dobutamine groups.

	Tilmicosin	Tilmicosin+Amiodarone	Tilmicosin+Amiodarone+Dobutamine
Survival time (minutes)	56.8±10.39	81.6±13.99	192±6.03*, #

* Statistically significant compared to the tilmicosin group (P<0.05).

Statistically significant compared to the tilmicosin+amiodarone group (P<0.05).

Table 2. Effect of tilmicosin administration on haemogram, troponin I, CK-MB and biochemical parameters (mean±SE).

Parameters	Control	Death
WBC(x10^9/L)	23.40±0.23^a	12.04±0.35^b
RBC(x10^{12}/L)	20.80±1.43^a	19.2±1.32^b
Hb(g/L)	10.12±0.69^a	8.92±0.61^b
Hct(%)	28.90±1.98^a	26.54±1.80^b
TroponinI(ng/L)	327±28.05^b	467±30.30^a
CK-MB(ng/mL)	5.79±0.92	7.23±0.25
Albumin(g/dL)	2.36±0.14^a	1.80±0.19^b
Total protein(g/dL)	6.88±0.46^a	5.28±0.49^b
AST(U/L)	63.6±3.53	59.0±2.88
ALT(U/L)	12.4±1.66	10.8±1.02
Triglyceride(mg/dL)	11.8±1.83^b	28.6±3.08^a
Cholesterol(mg/dL)	76.2±3.15	84.2±11.2
Urea(mg/dL)	42.2±2.22	69.4±13.8
Creatinine(mg/dL)	0.73±0.06^b	1.17±0.06^a

Table 3. Effect of tilmicosin+amiodarone application on haemogram, troponin I, CK-MB and biochemical parameters (mean±SE)

Parameters	Control	Death
WBC(x10^9/L)	22.86±0.47^a	7.90±0.53^b
RBC(x10^{12}/L)	19.84±0.13^a	17.62±0.65^b
Hb(g/L)	9.50±0.14^a	7.98±0.28^b
Hct(%)	27.14±0.57^a	23.78±0.86^b
TroponinI(ng/L)	403±83.1	519±37.1
CK-MB(ng/mL)	5.82±0.81^b	10.41±1.47^a
Albumin(g/dL)	2.28±0.07^a	1.82±0.12^b
Total protein(g/dL)	6.70±0.04^a	5.48±0.12^b
AST(U/L)	71.00±2.65	78.00±7.26
ALT(U/L)	11.80±0.86	12.60±1.33
Triglyceride(mg/dL)	17.60±1.47^b	27.4±1.63^a
Cholesterol(mg/dL)	59.20±3.43^a	43.8±1.11^b
Urea(mg/dL)	35.00±3.49	40.00±2.49
Creatinine(mg/dL)	0.73±0.03^b	1.11±0.08^a

Table 4. Effect of tilmicosin+amiodarone+dobutamine administration on haemogram, troponin I, CK-MB and biochemical parameters (mean±SE)

Parameters	Control	Death
WBC(x10^9/L)	22.75±0.92[a]	9.38±1.30[b]
RBC(x10^{12}/L)	16.08±0.79[a]	13.37±0.47[b]
Hb(g/L)	7.54±0.31[a]	5.98±0.18[b]
Hct(%)	20.84±1.81[a]	16.80±0.95[b]
TroponinI(ng/L)	464±43.61	507±42.60
CK-MB(ng/mL)	8.85±1.42	9.03±0.99
Albumin(g/dL)	2.50±0.07[a]	1.66±0.04[b]
Total protein(g/dL)	7.16±0.11[a]	4.84±0.23[b]
AST(U/L)	84.60±2.91	103±14.91
ALT(U/L)	13.00±1.38	11.20±3.00
Triglyceride(mg/dL)	22.60±4.32	22.40±2.54
Cholesterol(mg/dL)	59.60±5.09[a]	39.00±3.54[b]
Urea(mg/dL)	44.60±0.40	47.20±3.29
Creatinine(mg/dL)	0.71±0.04	0.87±0.05

DISCUSSION

Tilmicosin is a macrolide antibacterial drug that is widely used in respiratory system infections in animals except goats. The drug has a cardiotoxic effect, which causes death in goats (Giguère et al., 2013; Papich, 2016).

In the current study, the effects of tilmicosin on ECG, survival time, haemogram, and biochemistry, as well as treatment options for tilmicosin toxicity were investigated in goats. We observed that tilmicosin caused an increase in heart rate from the 10th minute (shortening the QT interval), worsening of clinical status after 20-30 minutes, CNS depression, respiratory distress, lying on the sternum, and death. In addition, ventricular tachycardia and ventricular fibrillation were observed right before death. Except for a decrease in heart rate in the treatment groups, other findings were alike at near-death. Amiodarone leads to increase vagal tonus within the first 20 minutes and causes bradycardia (Dias da Silva et al., 2002). Some drugs in different therapeutic classes affect heart function. Electrocardiogram recordings are important in clinical toxicity studies as they allow monitoring of drug-induced changes in cardiac conductivity or rhythmicity. The QT interval depends upon the heart rate, which is closely related to the RR interval. The QT interval is reported to be of potential clinical value because of its association with ventricular arrhythmias (Hanton et al., 2001). The heart is the important organ of acute tilmicosin toxicity. Positive chronotropy and negative inotropy are observed in high doses of tilmicosin-induced cardiotoxicity (Jordan et al., 1993; Main et al., 1996; Christodoulopoulos 2009). Shortening of the QT interval may be related to the blocking of Ca^{++} channels (CVMP, 2009; Lust et al., 2011). A decrease in the stroke volume of the heart has been reported in donkeys treated with tilmicosin. Significant increase in the left ventricular volume at the end of systole in the early period, 30 minutes after tilmicosin administration, causes systolic failure, which indicates the deterioration of the contraction and/or pumping function of the heart (Youssef et al., 2016). There are no experimental studies on tilmicosin cardiotoxicity in goats. In the study in which 10 mg/kg subcutaneous and intravenous infusion were administered to goats (2-3 years old) and pharmacokinetic parameters were examined, no death was reported, but clinical signs showing acute cardiac toxicity were reported with slow intravenous infusion of tilmicosin dilute solution. While goats returned to clinical normality within 25 minutes after infusion, no adverse effects were noted after subcutaneous injection (Ramadan, 1997; El Sayed et al., 2016). Approximately 1 minute after injection of tilmicosin (15 mg/kg, subcutaneous), increased heart rate and CNS depression followed by mild respiratory distress with lying on the sternum were reported in a 15-day-old lamb (Christodoulopoulos 2009). Coskun*et al.*, (2012) reported that younger goats died within 1 hour after subcutaneous tilmicosin administration, but older goats did not die. When these studies are evaluated as a whole, it is concluded that tilmicosin administered subcutaneous at a dose of 10 mg/kg to goats >2 years old does not cause deaths. In the current study, clinical findings such as increased heart rate, CNS depression, coldness in the nose-mouth-extremities and respiratory distress occurred more severely and in a shorter time

in the tilmicosin group than in other groups, which may have shortened the survival time. The reason for the difference between our findings and previous studies may be the difference in goat breeds and age because the drug sensitivity of goat breeds is different (Zweers-Zeilmaker et al., 1996).

While tilmicosin caused death within the first hour, it was observed that amiodarone increased this time approximately 1.5 times and amiodarone+dobutamine approximately 3.5 times. Although there is no specific antidote used in tilmicosin cardiotoxicity (Diaz, 2014), there are studies that reported that the mortality rate at the lethal dose of tilmicosin in rats was reduced using amiodarone and that dobutamine was beneficial for sublethal dose of tilmicosin in dogs (Main et al., 1996; Er et al., 2014). Amiodarone is successfully used in AV tachycardia because it causes a decrease in heart rate after intravenous administration (Vassallo and Trohman, 2007). It is also reported to reduce sudden deaths after acute myocardial infarction (Heidenreich et al., 2002). Inotropes increase cardiac contractility andimprove renal perfusion. Therefore, inotropic therapy may be beneficial in patients with severely reduced cardiac output, systemic hypoperfusion and end-organ dysfunction (GinwallaandTofovic, 2018). We observed that amiodarone+dobutamine was able to prolong survival more than amiodarone alone. This may be related to the fact that amiodarone decreases the increased heart rate and dobutamine increases the decreased contractility because dobutamine exerts a positive inotropic effect through alpha 1 adrenergic receptor in the heart (Vallet et al., 1991).

In this study, treatments could not prevent a decrease in haemogram parameters caused by tilmicosin. In a study in mice, when tilmicosin was administered at a dose of 40 mg/kg, it caused a significant decrease in RBC, HCT and HGB values, while the WBC value was found to be like the control. In the 20 mg/kg dose, the HGB value decreased significantly, while the WBC, RBC and HCT values were found to be like the control. In addition, while it caused a decrease in WBC and RBC values in broiler chicken, HGB value did not change (Elsayed et al., 2014;Gheith et al., 2015). It is stated that the decrease in RBC and haematocrit values indicate bone marrow dysfunction caused by tilmicosin, and high creatinine and urea levels indicate renal dysfunction caused by tilmicosin. Renal dysfunction can cause decreased production of erythropoietin, a key hormone in RBC synthesis (Gheith et al., 2015). While tilmicosin caused a statistically significant increase in triglyceride and creatinine levels and an insignificant increase in urea levels, it caused a decrease in albumin and total protein levels (Table 2). In the tilmicosin+amiodarone group, albumin, total protein and cholesterol levels were decreased, and triglyceride and creatinine levels increased (Table 3). In the tilmicosin+amiodarone+dobutamine group, a decrease in albumin, total protein and cholesterol levels could not be prevented, while an increase in triglyceride and creatinine levels was prevented (Table 4). The decrease in triglyceride may be related to the activation of the lipase enzyme by dobutamine, caused by stimulation of beta 1 and 3 adrenergic receptors (Kayaalp, 2009). It has been reported that when tilmicosin is administered at high doses, it causes a decrease in albumin and total protein levels (Elsayed et al., 2014;Gheith et al., 2015). Hypoproteinaemia and increased triglyceride, urea and creatinine levels may indicate hepatorenal toxicity.

Tilmicosin administration caused an increase in troponin I ($P \leq 0.05$) and CK-MB ($P > 0.05$) levels. Amiodarone blocked the increase in troponin but could not prevent the increase in CK-MB. Amiodarone+dobutamine administration prevented the increases in both parameters ($P \leq 0.05$, Table 4). Cardiac injury markers are released into the bloodstream from damaged heart muscle cells. The extent of muscle damage is assessed by the blood levels of these markers. Tilmicosin shows different degrees of cardiotoxic effect in various animal species depending on the route of administration and dose. It is stated that the cardiotoxic effect is alleviated as a result of lessening the increase in troponin and CK-MB levels due to the administration of tilmicosin (Yazar et al., 2001; Elazab et al., 2014; Cetin, 2019). It has reported that troponin is a specific marker of heart damage, while CK-MB is not (Chen et al., 1999). The reduction in tilmicosin-mediated troponin increase in the treatment groups suggests that dobutamine and amiodarone partially prevent heart damage.

CONCLUSION

The differences in breed and species of animals are important factors in the drug response. Goats were chosen for this study due to their sensitivity to tilmicosin. Amiodarone+dobutamine prolonged the short survival time associated with cardiotoxicity induced by tilmicosin more than amiodarone. While troponin and CK-MB levels, which are indicators of heart damage, increased with tilmicosin administration, these

increases were mitigated with amiodarone+dobutamine treatments. According to the results of the study, it can be stated that in cases of tilmicosin poisoning, especially in goats, the application of amiodarone+dobutamine may further increase the survival time, provided adequate medical support and sedative treatment is available. In addition, new research is needed to develop treatments that can be used in cases of tilmicosin poisoning.

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CONFLICT OF INTEREST

None declared.

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