Original Article

Echocardiographic alterations after administration of azithromycin in donkeys: An experimental crossover study

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Abstract

Cardiotoxicity and impairment of cardiac function are mostly diagnosed by echocardiography and based on objective metrics of cardiac function. The aim of the present study is to investigate the effect of azithromycin on the echocardiographic characteristics in healthy donkeys. Ten healthy donkeys were enrolled in a prospective crossover study. The study included two groups: (1) a placebo (normal saline, NaCl 0.9%), and (2) azithromycin (at a dose of 5 mg/kg body weight). A 2.0-3.9 MHz phased-array transducer was used for echocardiographic examination. Echocardiographic examinations were performed for donkeys before treatment (T0) and at 15, 30, 60, 90, 120, 180, and 240 min after azithromycin administration. In the azithromycin group compared to Placebo, the drug induced a significant increase in interventricular septal thickness in end-diastole (IVSTd) and interventricular septal thickness in end-systole (IVSTs) ($P < 0.05$), but it induced a significant decrease in left ventricular internal diameter (LVID) at end diastole (LVIDd) and at end systole (LVIDs) ($P < 0.01$). There was also a significant ($P < 0.05$) decrease in left ventricular posterior wall thickness at the end of diastole (LVPWd) and at the end of systole (LVPWs) compared with placebo. Left ventricular volume increased significantly ($P < 0.05$) at the end diastole (EDV), and at the end systole (ESV). Fractional shortening (FS%) decreased significantly ($P < 0.05$) in donkeys receiving azithromycin compared to placebo. In conclusion, azithromycin in healthy donkeys induces transient and mild effects on echocardiographic parameters with fewer overt clinical signs. Further studies are needed to evaluate the efficacy of this drug, specifically in equines with underlying cardiac disease.

Keywords: Arrhythmia, Azithromycin, Cardiac function, Donkeys, Macrolides

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Introduction

Azithromycin is a bacteriostatic and bactericidal antimicrobial that suppresses protein synthesis by binding to the 50S ribosome but has no effect on mRNA translation or nucleic acid synthesis (Shepard and Falkner, 1990). It has recently been studied in dairy cows, horses, dogs, and cats for the treatment of pyogenic and intracellular pathogens (Lucas *et al.*, 2010).

Azithromycin inhibits the inflammatory process by activating CD4+ T cells and altering the levels of several pro-inflammatory cytokines such as interleukin (IL)-1β, IL-8, IL-17, and tumor necrosis factor alpha (Ratzinger *et al.*, 2014). It is used to treat respiratory tract illnesses in foals caused by *Rhodococcus equi* infection (Carter *et al.*, 1995) with minimal cardiovascular toxicity (Lu *et al.*, 2015).

Macrolides (azithromycin and clarithromycin) are important antibiotics for the treatment of upper respiratory tract infections (RTIs). They are widely used for empirical therapy of equine RTIs due to their broad-spectrum activity against gram-positive cocci such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*, as well as atypical pathogens such as *Hemophilus influenzae* and *Moraxella catarrhalis* (Goebel *et al*., 2022; Mainguy-Seers *et al.*, 2022).

Azithromycin regimens of 3 days (500 mg single dose per day) or 5 days (500 mg on the first day, 250 mg on subsequent days) were clinically and microbiologically as effective as prolonged treatment with other macrolides in human studies (Blasi *et al.*, 2007). This is because of the prolonged half-life, excellent tissue penetration, and high tissue concentrations, which can be more than 100 times higher than those in the bloodstream (Blasi *et al*., 2007).

The pharmacokinetics of macrolide antibiotics in foals revealed that these drugs have unique pharmacokinetic features such as rapid and extensive distribution and long persistence in pulmonary epithelial lining fluid (Villarino and Martín-Jiménez, 2013). For azithromycin, the body clearance was 10.4 ml/min × kg, and the apparent volume of distribution at steady state was 18.6 L/kg. After i.g. administration, the time to peak serum concentration was 1.8 hours, and bioavailability was 56% (Jacks *et al.*, 2001).

To date, limited information is available on the clinical efficacy and safety of azithromycin in horses, with limited information available on adult donkeys. In this regard, the study conducted by Davis *et al* (2002) evaluated the distribution of azithromycin in the plasma, polymorphonuclear leukocytes, and alveolar cells of horses following a single oral administration of 5 mg/kg body weight IV and 10 mg/kg body. Azithromycin has also recently been studied orally in ponies with various pulmonary lesions at a dose of 10 mg/kg (Goebel *et al*., 2022; Mainguy-Seers *et al.*, 2022).

Clinical data have shown that azithromycin could likely have adverse effects on foals, including an increased risk of diarrhea, overheating, and respiratory distress (Patel *et al*., 1996; Stratton-Phelps *et al.*, 2000). A study on dogs and cats showed that the most common side effects of azithromycin include stomach pain, vomiting, diarrhea, and, in rare cases, angioedema and jaundice (Beaudoin *et al*., 2023).

In an animal model, a pivotal study investigated the cardiotoxic effects of azithromycin in a rat model. The findings indicated that a five-day administration of azithromycin led to significant weight alterations in the electrocardiogram (El-Shitany and El-Desoky, 2016). More serious side effects may also occur, such as ventricular tachycardia and renal dysfunction (Guardabassi *et al*., 2008). Single injection of macrolides antibiotic induced myocardial degeneration in rats with an increase of cardiac muscle derived enzymes Single injection of macrolides antibiotic induced myocardial degeneration in rats with an increase of cardiac muscle derived enzymes (Kart *et al.*, 2007).

Echocardiography remains the imaging technique of first choice to rule out the presence of structural heart disease and assess left and right ventricular function (Delgado *et al*., 2016). An echocardiogram showing global cardiac hypokinesia in a man injected with tilmicosin (Sheikh *et al.*, 2025). Moreover, an experimental study on tilmicosin revealed an echocardiographic abnormality in donkeys (Youssef *et al.*, 2016).

Both donkeys and horses have respiratory diseases that can be treated with macrolide antibiotics. No information is available on the use of azithromycin in donkeys, and there is no evidence of adverse effects on cardiac function. Therefore, the aim of the present study was to evaluate the changes in cardiac function after administration of azithromycin in donkeys. We hypothesized that the administration of injectable azithromycin to donkeys could adversely affect clinical parameters and cardiac function.

Materials and Methods

Donkeys: Ten clinically healthy donkeys (*Equus asinus*) were used in this randomized crossover study. Donkeys were related to experimental animals at the Faculty of Veterinary Medicine, Mansoura University. The donkeys were between 9 and 13 years of age (mean ± standard deviation, 10.8 ± 1.6 years) and had a body weight between 120 and 200 kg (mean ± standard deviation, 151 ± 25.3 kg). The animals underwent a 14-day acclimation period. Subsequently, all donkeys underwent thorough physical examination and echocardiographic assessment to ensure their clinical health status. Clinical and echocardiographic examinations revealed that none of the donkeys had any cardiovascular abnormalities or signs of systemic disease. All animals were housed in straw-padded stalls for two weeks before the start of the experiment and were fed 1 kg of hay/100 kg body weight twice daily plus 0.5 kg of concentrate and full access to water.

Ethical approval: The Mansoura University Animal Care and Use Committee gave its approval to this study (VM.R20.12.111). The Department of Internal Medicine and Infectious Diseases, Faculty of Veterinary Medicine, Mansoura University, Egypt, is where this study was carried out. Donkeys were housed in the Mansoura University veterinary medicine faculty farm at the conclusion of the trial.

Study design: The two treatment groups in this randomized crossover study were azithromycin

(Zithromax 500 mg for intravenous infusion; Pharmacia & Upjohn Company, Kalamazoo, Pfizer Inc., USA) and placebo (normal saline, NaCl 0.9%; El-Nasr Pharmaceutical Chemicals Co., Egypt). In accordance with the manufacturer's recommendations, 5 mg/kg body weight of azithromycin was diluted with 0.9% NaCl to a concentration of 2 mg/ml and then gently infused intravenously (Villarino and Martin-Jimenez, 2013). There were two weeks between the two treatments. Echocardiographic examination and cardiac function were evaluated for each donkey before treatment (T0) and at 15 (T15), 30 (T30), 60 (T60), 90 (T90), 120 (T120), 180 (T180), and 240 (T240) min after administration of azithromycin. Evidence of potential clinical adverse effects (e.g., changes in heart rate, cardiac rhythm, nervous signs, rectal temperature, respiratory rate, mucous membrane color, soft manure, and diarrhea) was observed and documented simultaneously.

Echocardiographic examination: A Digital Color Doppler Ultrasound System (iVis 60 Expert VET, Chison Medical Imaging Co., Ltd., China) with a 2.5 MHz phased-array scanning transducer and a maximum depth of 24.1 cm was used for echocardiographic evaluation. Transcutaneous echocardiographic examination was performed using previously reported standard procedures (Youssef *et al.*, 2016). An assistant lifted the forelimb cranially and laterally from the torso while echocardiography was performed in a standing position. To achieve the best quality standard pictures, the rotation, angulation, and placement of the phased-array transducer were assessed.

Echocardiographic measurements: As advised by the American Society of Echocardiography, echocardiography was carried out on frozen images on the screen utilizing the state-of-the-art technique (Schiller *et al.*, 1989). Echocardiography was done at the chordae tendineae level using the right parasternal long-axis four-chamber view and the right parasternal short-axis view. The previously described method (dos Santos Michima *et al.*, 2004; Reef, 1998) was used to take the following B-mode and guided M-mode measurements: left ventricular internal diameter at end-systole (LVIDs) and end-diastole (LVIDd), left ventricular posterior wall thickness at end-systole (LVPWs), and end-diastole (LVPWd) using the Cube Method; interventricular septal thickness at end-systole (IVSTs) and end-diastole (IVSTd) as well. In the meantime, B-mode and M-mode echocardiography were used to measure the left ventricular volume at end-diastole (EDV) and end-systole (ESV) using a predetermined formula (Hanton *et al.*, 1998). The formula SV = EDV-ESV was used to get the stroke volume (SV). Fractional shortening (FS) and ejection fraction (EF) were also assessed using the Teichholz method in B-mode and M-mode echocardiography, according to an established formula (Nyland and Mattoon, 2002).

Statistical analysis: The data were analyzed using SPSS for Windows software, version 22, USA. To ascertain if the data were normally distributed, the Kolmogorov-Smirnov normality test was employed. The mean and standard deviation for each variable at each time point were displayed since the data were Gaussian and so normally distributed. A generic linear model with repeated-measures analysis of variance was used to evaluate how echocardiographic parameters changed over time and with treatment. Evidence of time × treatment interactions and within-group differences was assessed using the Wilks' lambda test. A t-test was used to identify which group was statistically different at each time point when Wilks' lambda test indicated a statistically significant difference between groups. At $P < 0.05$, differences were deemed significant.

Result

Azithromycin administration had a remarkable effect on various physiological parameters. Notably, a significant ($P < 0.05$) decrease in heart rate (at T120), respiratory rate (at T90), and rectal temperature (at T90) was observed when compared to a placebo (Tables 1–3). No other discernible signs or adverse effects associated with azithromycin use were documented.

Figures 1–9 show the effects of time, treatment, and the time × treatment interaction following azithromycin administration in donkeys.

In general, the use of injectable azithromycin had a significant ($P < 0.05$) time effect on the echocardiographic parameters, including IVST, LVID, LVPW at end-diastole and end-systole, EDV, ESV, and FS%. Azithromycin induced a significant ($P < 0.05$) increase in IVSTd at T120 compared with placebo (Fig. 1). There was a significant ($P < 0.05$) increase in IVSTs in donkeys that received azithromycin compared with placebo at T30, T60, T90, and T120 (Fig. 2).

Azithromycin induced a significant ($P < 0.01$) increase in LVID when compared to placebo at end-diastole at T60, T90, T120, T180, and T240 (Fig. 3), and at end-systole at T30, T60, T90, and T120 (Fig. 4).

There was a significant ($P < 0.05$) decrease in LVPW at end-diastole at T30, T60, T180, and T240 (Fig. 5), and at end-systole at T90, T120, T180, and T240 (Fig. 6) when compared with placebo.

Left ventricular volume showed a significant ($P < 0.05$) increase at end-diastole (EDV) at T60, T90, T120, and T180 (Fig. 7), and at end-systole (ESV) at T90, T120, and T180 (Fig. 8) when compared to placebo.

The FS (%) decreased significantly in donkeys receiving azithromycin when compared to the placebo ($P < 0.05$). FS (%) decreased at T120, T180, and T240 (Fig. 9). However, other echocardiographic parameters, such as SV and EF, showed a non-significant decrease in the examined donkeys after administration ($P > 0.05$).

Table 1 Time course of heart rate (means ± SD) in donkeys received injectable azithromycin compared with placebo.

Groups	Time After Administration (min)							
	T0	T15	T30	T60	T90	T120	T180	T240
HR								
Placebo	39.60 ± 3.09	40.10 ± 3.21[a]	40.60 ± 1.89[a]	39.70 ± 2.90[a]	39.40 ± 2.31[a]	40.30 ± 2.58[a]	39.30 ± 0.94[a]	40.70 ± 1.88
Azithromycin	40.80 ± 3.42	37.10 ± 3.07[b]	33.70 ± 2.90[b]	30.70 ± 2.26[b]	27.90 ± 2.07[b]	24.60 ± 2.75[b]	34.20 ± 3.96[b]	40.20 ± 2.89

[a,b] Means with different superscript letters are significantly different at $P < 0.05$. HR: heart rate.

Table 2 Time course of respiratory rate (means ± SD) in donkeys received injectable azithromycin compared with placebo.

Groups	Time After Administration (min)							
	T0	T15	T30	T60	T90	T120	T180	T240
RR								
Placebo	17.10 ± 2.80	20.70 ± 4.76[a]	21.00 ± 2.78[a]	19.10 ± 1.91[a]	20.80 ± 3.88[a]	18.00 ± 3.01[a]	19.90 ± 1.37[a]	20.40 ± 3.74
Azithromycin	18.00 ± 3.94	15.90 ± 3.03[b]	12.90 ± 1.79[b]	10.50 ± 1.17[b]	8.40 ± 1.34[b]	10.20 ± 2.48[b]	16.60 ± 2.79[b]	19.70 ± 3.59

[a,b] Means with different superscript letters are significantly different at $P < 0.05$. RR: respiratory rate.

Table 3 Time course of rectal temperature (means ± SD) in donkeys received injectable azithromycin compared with placebo.

Groups	Time After Administration (min)							
	T0	T15	T30	T60	T90	T120	T180	T240
Body Temperature								
Placebo	36.89 ± 0.39	36.92 ± 0.42	37.19 ± 0.32[a]	36.99 ± 0.29[a]	36.92 ± 0.29[a]	36.93 ± 0.23[a]	36.93 ± 0.24[a]	37.03 ± 0.23
Azithromycin	37.04 ± 0.53	36.84 ± 0.48	36.63 ± 0.38[b]	36.39 ± 0.40[b]	36.08 ± 0.10[b]	36.14 ± 0.25[b]	36.56 ± 0.39[b]	37.09 ± 0.26

[a,b] Means with different superscript letters are significantly different at $P < 0.05$.

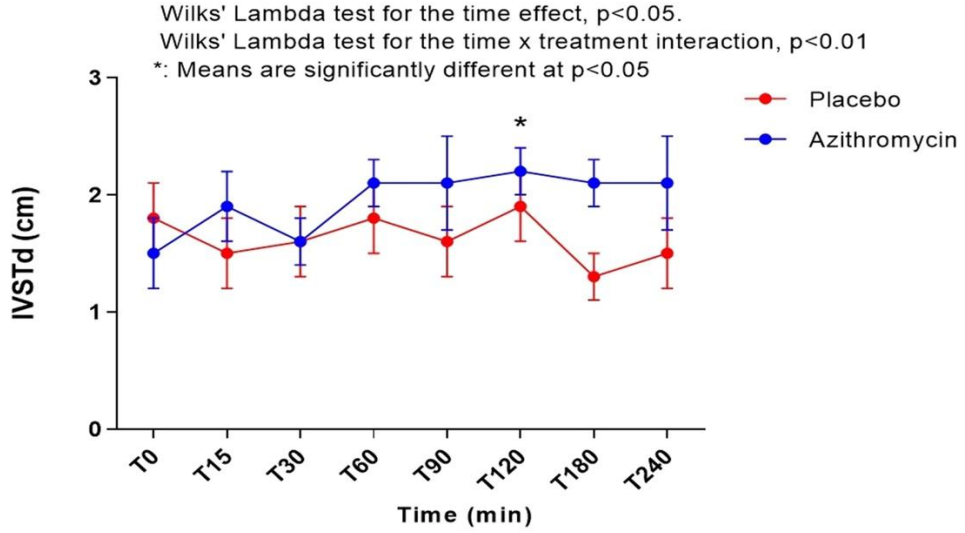

Figure 1 Interventricular septal thickness at end–diastole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

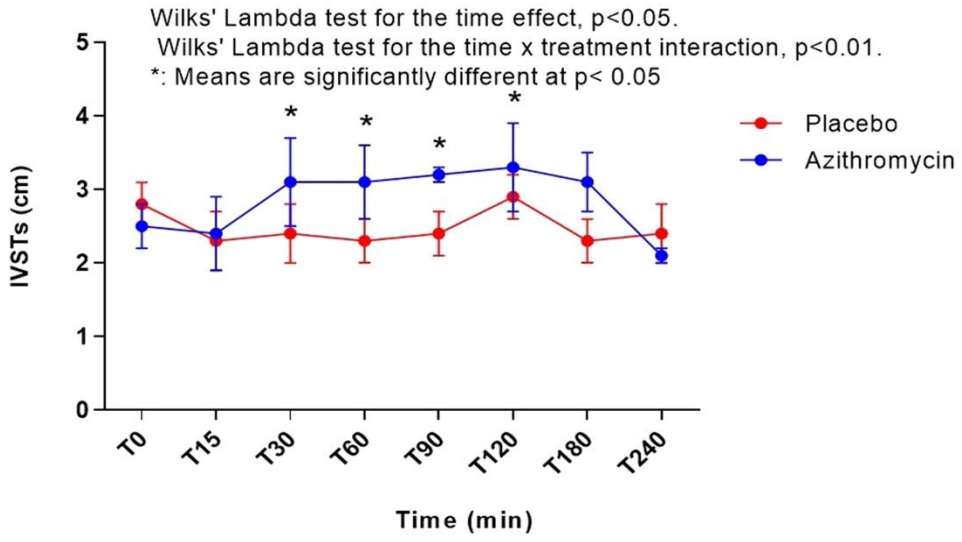

Figure 2 Interventricular septal thickness at end-systole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

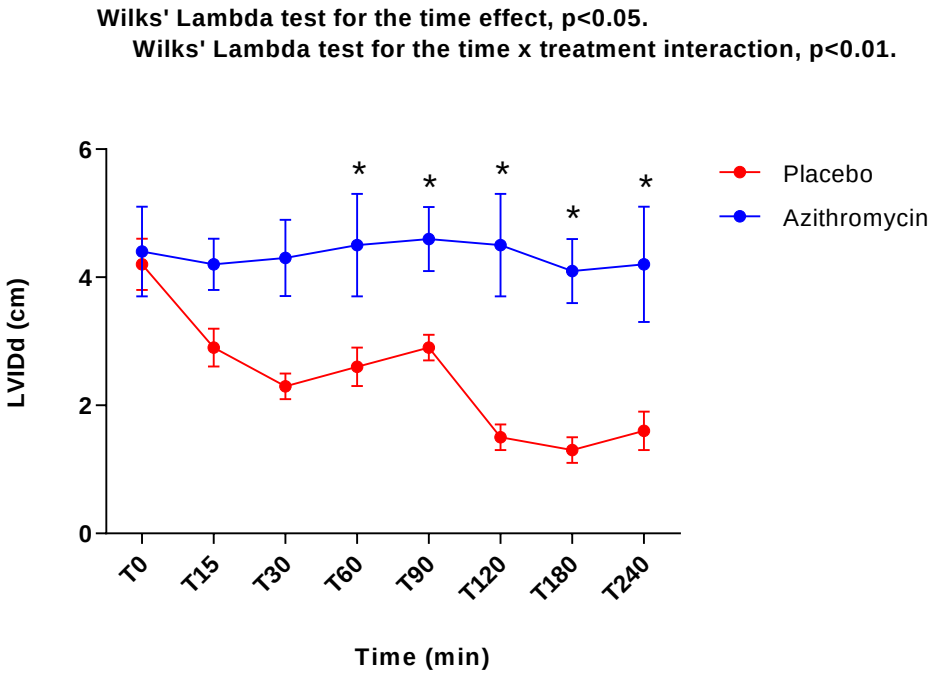

Figure 3 Left ventricular internal diameter at end–diastole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

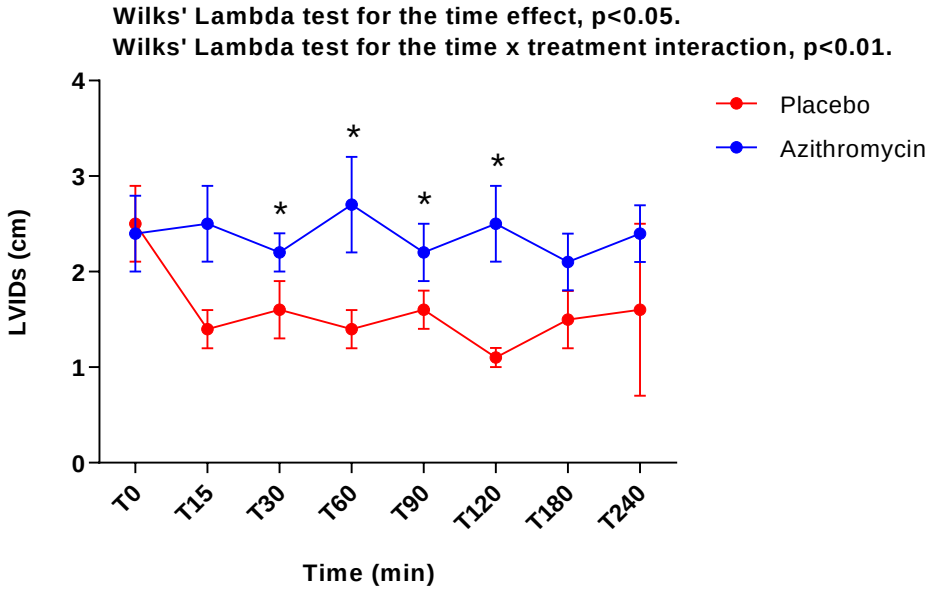

Figure 4 Left ventricular internal diameter at end-systole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

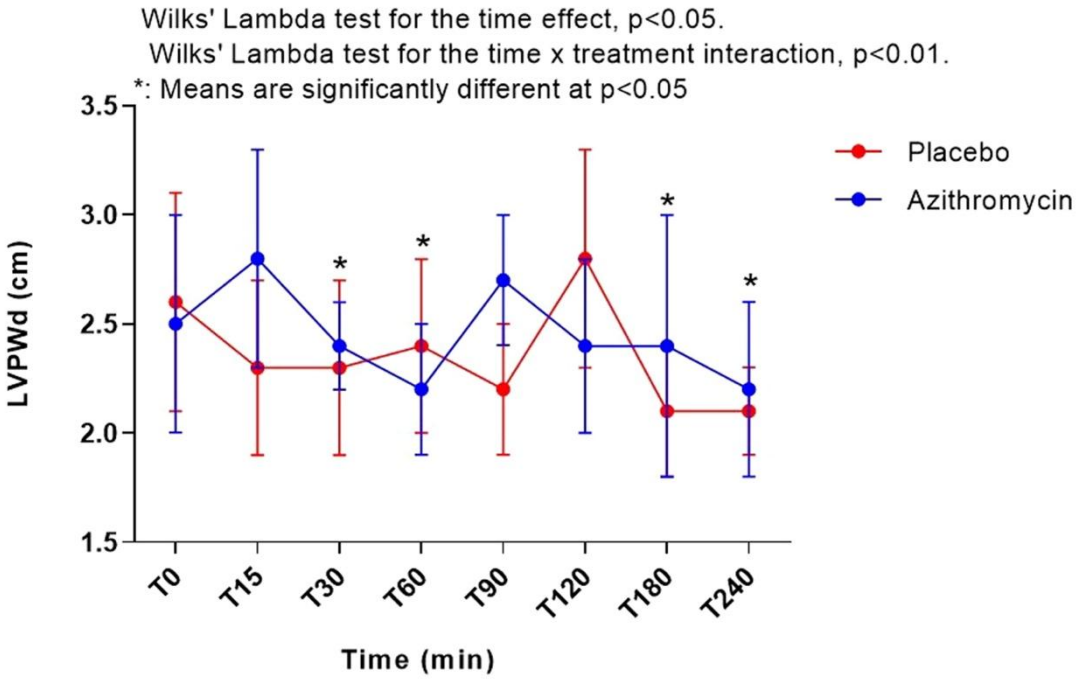

Figure 5 Left ventricular posterior wall at end–diastole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

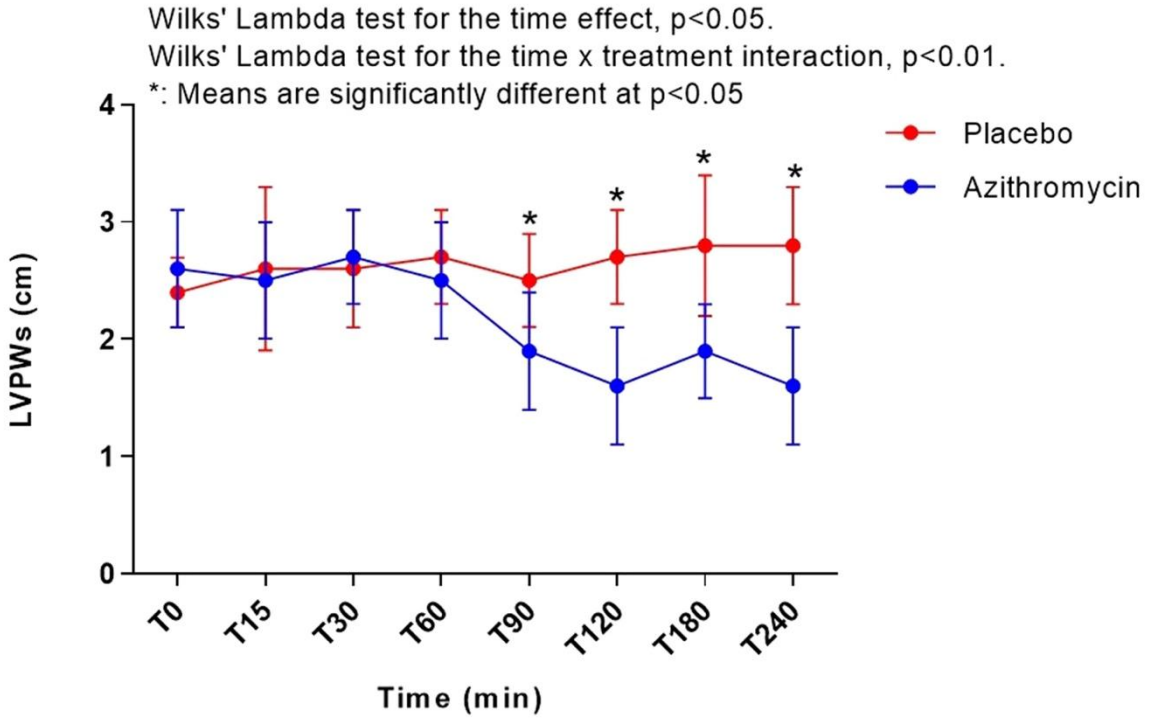

Figure 6 Left ventricular posterior wall at end–systole (cm; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

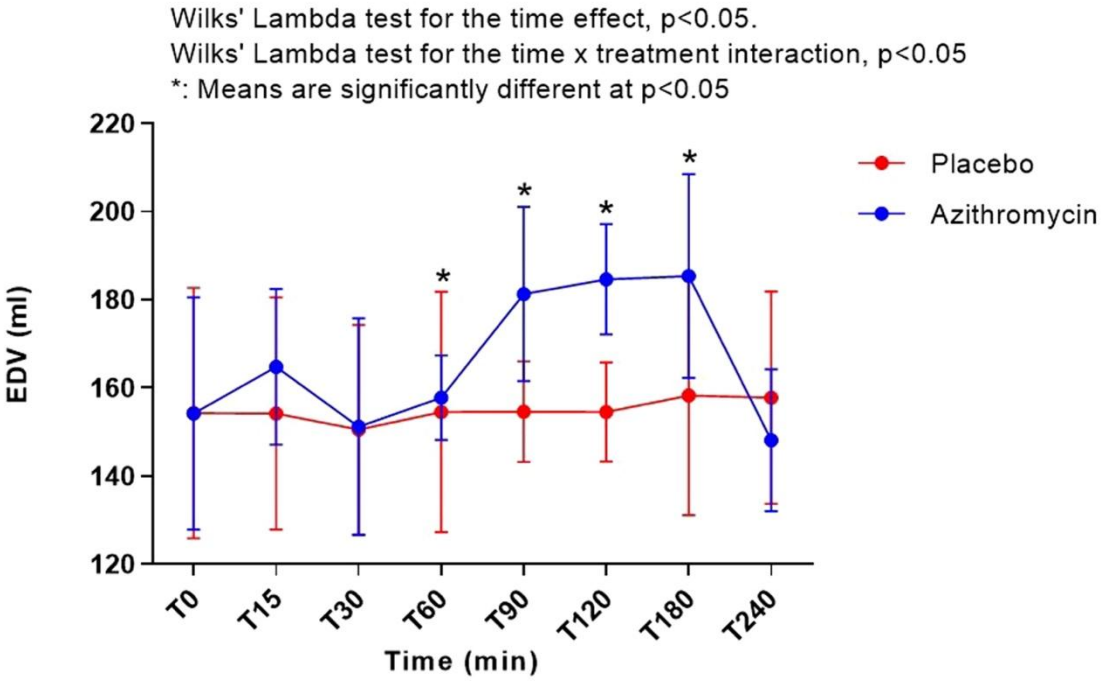

Figure 7 Left ventricular volume at end–diastole (mL; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

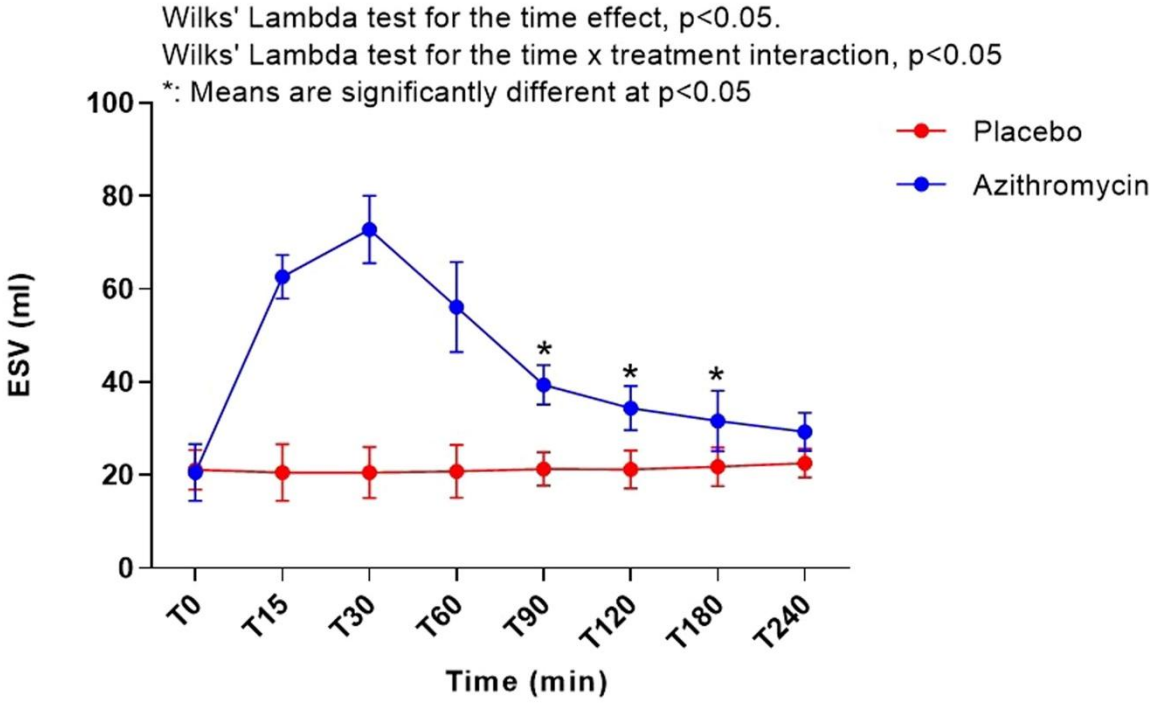

Figure 8 Left ventricular volume at end–systole (mL; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

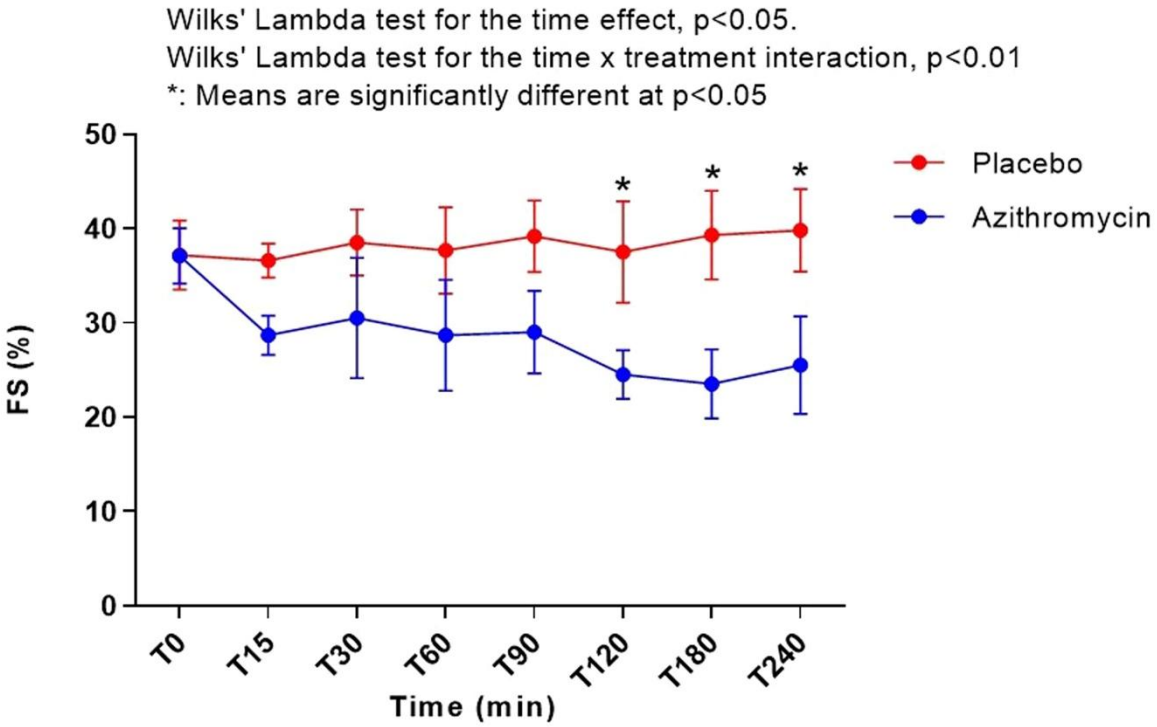

Figure 9 Fractional shortening percentage (%; mean ± standard deviation) after administration of azithromycin in donkeys at different time points.

Discussion

Antimicrobial therapy is an important module of equine medicine used to treat known or suspected bacterial infections, as well as to prevent postoperative and secondary infections. Azithromycin is approved for the treatment of a variety of respiratory tract infections in horses (Goebel *et al*., 2022; Mainguy-Seers *et al*., 2022). However, 14.8% of the isolated *Rhodococcus equi* have been found to be resistant to such drugs (Erol *et al*., 2020).

Azithromycin can cause bradycardia, which can lead to a potentially deadly irregular heart rhythm (Goldstein *et al*., 2006). The Food and Drug Administration took note of a 2012 study that found azithromycin may increase the risk of death, particularly in patients with heart problems (Ray *et al*., 2012). In the present study, we used echocardiography to assess the cardiac dimensions and functions in donkeys after administration of azithromycin. In human medicine, echocardiography remains the imaging technique of first choice to rule out the presence of structural heart disease and assess left and right ventricular function. Moreover, advances in strain echocardiography have provided important insights into the mechanisms of ventricular arrhythmias (Delgado *et al*., 2016).

IVSTs and IVSTd were significantly increased in azithromycin-treated donkeys after administration. Increased interventricular septal thickness can impair left ventricular (LV) function by reducing its pumping efficiency. This finding could imply prolonged ventricular repolarization as a result of left ventricular myocardial dysfunction caused by impaired heart pumping function (Gehlen *et al*., 2004). Furthermore, LVID and LVPW were significantly decreased in the azithromycin group. Fluctuations in wall thickness imply pseudohypertrophy, a reversible , and an increase in wall thickness that has also been linked to diminished ventricular dimensions (Di Segni *et al*., 1997). In cases of conditions like hypertrophic cardiomyopathy, the IVS may be disproportionately thick compared to the LV free wall. It has been found that azithromycin use was associated with an increased risk of ventricular arrhythmia when compared with non-use (Trifirò *et al*., 2017).

In the present investigation, LVEDV was significantly increased after injection of azithromycin. This increase may be attributed to the transitory increase in ventricular compliance with resultant heart failure (Le Pailleur C, 1977). Furthermore, the left ventricular volume at end-systole was significantly increased in azithromycin-treated donkeys at various time points after administration, indicating a state of systolic failure caused by impaired heart contractility, and affected by increased left ventricular cavity size. In general, the left ventricular volume is particularly. This is a useful tool for assessing global left ventricular function because it allows the evaluation of minor changes in left heart morphology and myocardial function (thickness and diameter of the myocardium and chambers) (Stadler and Robine, 1996).

The fractional shortening percentage is the most basic metric of left ventricular performance and pumping function of the heart (Walders and Gehlen, 2014). FS% in azithromycin-treated donkeys was low, indicating reduced cardiac contractility. Increased wall stress and reduced contractile function are considered the primary causes of FS reduction in systolic myocardial failure. However, a study conducted on the effect of tilmicosin phosphate on the heart in donkeys revealed a significant decrease in FS, EF, and SV (Youssef *et al*., 2016). In the present study, FS showed

only a significant decrease. Significant decreases in EF and SV were observed, but non-significantly. Our result is supported by the findings of a study of a human treated with tilmicosin. This study showed non-significant variation of EF and stroke volume (Sheikh *et al.*, 2025). Moreover, in human medicine, left ventricular EF may be normal in a large number of patients who are at risk of ventricular arrhythmias (Delgado *et al.*, 2016).

Regarding the limitations of this research, this study focused only on the immediate effects of azithromycin on the heart (using one dosage of the drug) and did not investigate any long-term consequences. Furthermore, considering the limited sample size of donkeys used in this study, further research with a larger population is necessary to validate these findings and provide more comprehensive insights into the impact of drugs on the cardiovascular health of donkeys.

In conclusion, Azithromycin in healthy donkeys induces transient and mild effects on cardiac function with fewer overt clinical signs. Further studies are needed to evaluate the efficacy of this drug, specifically in equines with underlying cardiac disease.

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Conflict of interest statement: Authors declare that there is no conflict of interest.

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