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Original Research

Effects of Tilmicosin Phosphate Administration on Echocardiographic Parameters in Healthy Donkeys (*Equus asinus*): An Experimental Study

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ABSTRACT

The aim of this study was to evaluate the effect of tilmicosin on echocardiographic measurements in donkeys. For this purpose, placebo and tilmicosin 30% (10 mg/kg) were administered subcutaneously to clinically healthy donkeys (n = 10) in a randomized prospective crossover study. Cardiac functions were evaluated by echocardiography using a 2.5-MHz curved-linear transducer at 0, 15, 30, 60, and 120 minutes after administration. Examination was carried out at 3 to 5 intercostal spaces, and measurements were obtained at three planes of images. Tilmicosin induced a significant decrease in fractional shortening percentage (FS%) at 30 minutes after treatment ($P < .05$), but ejection fraction percentage (EF%) and stroke volume (SV) were decreased at 60 minutes after treatment ($P < .05$). However, left ventricular volume at end-systole (LVESV) was increased when compared to placebo at 30, 60, and 90 minutes after administration ($P < .05$). Left ventricular volume at end-diastole (LVEDV) was increased at 60 minutes after treatment ($P < .05$). There was a positive correlation between FS% and EF% ($r = 0.89$, $P < .01$), LVESV and left ventricle internal diameter at systole (LVIDs; $r = 0.97$, $P < .01$), and SV and LVEDV ($r = 0.56$, $P < .01$). However, there was negative correlation between LVESV and EF% ($r = -0.41$, $P < .05$), ESV and FS% ($r = -0.44$, $P < .05$), LVIDs and EF% ($r = -0.43$, $P < .05$), and LVIDs and FS% ($r = -0.47$, $P < .05$). The present results indicate that tilmicosin could induce transient and short-lasting changes of cardiac function in donkeys.

1. Introduction

Tilmicosin, a macrolide antibiotic, is usually used in food animals for treatment of respiratory diseases associated with *Mannheimia haemolytica* and *Pasteurella multocida* [1–3]. In foals, tilmicosin showed various activity *in vitro* against most *Streptococcus* spp., *Staphylococcus* spp., *Actinobacillus* spp., and *Pasteurella* spp., and *Rhodococcus equi* [4–7]. In addition, tilmicosin exerts an anti-inflammatory effect via modulating the synthesis of many mediators and cytokines involved in the inflammatory process [8].

The use of the injectable tilmicosin product has been associated with acute cardiac toxicity in both human and animals [9–11]. In experimental animals, tilmicosin has been documented to cause cardiac toxicity and collapse [12,13]. In dogs, the adverse cardiovascular was evident with single dose of 5 mg/kg [9]. In cattle, the adverse effect is dose dependent [14], and a dose rate of 50 mg/kg could cause small foci of necrosis in the left ventricular papillary muscle of the heart [15]. Subcutaneous injection of tilmicosin in cattle causes inflammation at the injection site, but the severity of reaction is dose dependent [16]. In horses, tilmicosin at 10 mg/kg caused severe reactions at the injection sites including vascular collapse and transient

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swelling [17]. However, tilmicosin at 50 to 70 mg could increase cardiac muscle–derived enzymes in mice only [18].

The adverse effect of tilmicosin on the heart has been recognized through clinical findings, postmortem findings [19], increased serum level of cardiac muscle–derived enzyme, creatinine kinase [20], and other biochemical alterations [18].

In equines, echocardiography is the most acceptable tool for evaluation of the cardiac anatomy and functions [21–24]. In addition, via echocardiography, determination of the cardiac performance of clinically healthy animals and diagnosis of any cardiac pathologic conditions can be accomplished [25,26].

The donkey suffers from a similar range of respiratory diseases as the horse; however, there are a number of subtle variations, knowledge of which can influence the success of treatment [27]. In donkeys, there are no available data about the use of tilmicosin and the evidence of adverse effect on the cardiac function. Consequently, the objective of the present study was to evaluate the effect of single dose of tilmicosin on cardiac functions in donkeys via echocardiography.

2. Materials and Methods

2.1. Animals

Ten, clinically healthy donkeys (*Equus asinus*) were used in a randomized crossover study. The age of donkeys was 9 to 13 years (mean ± standard deviation, 10.8 ± 1.6 years), and their body weight was 120 to 200 kg (mean ± standard deviation, 151 ± 25.3 kg). None of those donkeys had cardiovascular disorders or any evidence of systemic diseases based on clinical and echocardiographic examination. Two weeks before starting the study, each donkey was stabled on straw-bedded boxes and fed on 1-kg hay/100 kg and 0.5-kg concentrate twice daily with unlimited access to water. This study was carried out at the Department of Internal Medicine and Infectious Diseases, Faculty of Veterinary Medicine, Mansoura University, Egypt. The study was approved by the Animal welfare and Ethics Committee, Faculty of Veterinary Medicine, Mansoura University.

2.2. Study Design

A randomized crossover experimental study incorporated two treatment trials, the placebo (normal saline, NaCl 0.9%; El-Nasr Pharmaceutical Chemicals Co, Egypt) and the tilmicosin (Pneumotac; ADWIA Pharmaceuticals Co S.A.E. 10th of Ramadan City, Egypt). Therapeutic dose of tilmicosin 30% was injected subcutaneously (10 mg/kg). Saline and tilmicosin were administered subcutaneously at the side of the neck with equal volume. According to the pharmacokinetics of tilmicosin in horses [17], the interval between the two treatments was 1 week. Echocardiographic examination and cardiac indices were evaluated for each donkey before treatment and at 15, 30, 60, and 120 minutes after treatment. During the monitoring periods, there was no access to food or water. In addition, the evidence of clinical adverse effects as injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, and death was observed during the monitoring period after the administration of tilmicosin.

2.3. Ultrasonographic Examination

First, donkeys were restrained in stocks without any sedation, and the chest was clipped at third to the fifth intercostal spaces just caudal to the triceps muscle mass, and from 3 to 5 cm below the olecranon to 5 to 10 cm above it. This area was cleaned with alcohol, and then, coupling gel was applied to enhance the contact with the probe. Transcutaneous echocardiographic examinations were performed according to standard methods [23,28,29] and the recommendations of the American Society of Echocardiography [30]. Echocardiographic examination was carried out using a 2.5-MHz curved-linear transducer (CHISON Digital Color Doppler Ultrasound system, iVis 60 EXPERT VET; CHISON Medical Imaging Co, Ltd, China). The location, rotation, and angulation of the transducer were considered to obtain the standard images. On echocardiographic examination, three image planes were included: right parasternal long-axis two-dimensional four-chamber view, left parasternal long-axis two-dimensional five-chamber view, and right parasternal short-axis view. Once the optimal imaging plane had been determined, both the cardiac indices were calculated using the Cube method and cardiac function using the Teichholz method. In all echocardiographic examination, the cardiac measurements were obtained by the same person. In addition, heart rate and respiratory rate were counted at each time point for each donkey.

2.4. Cardiac Function

The B-mode and guided M-mode measurements were obtained according to the methods described by Amory et al. [29]. Interventricular septal thickness at end-systole (IVSTs), interventricular septal thickness at end-diastole (IVSTd), left ventricular internal diameter at end-systole (LVIDs), left ventricular internal diameter at end-diastole (LVIDd), left ventricular posterior wall thickness at end-systole (LVPWs), and left ventricular posterior wall thickness at end-diastole (LVPWd) were assessed through the Cube method. Meanwhile, the left ventricular volume at end-diastole (LVEDV) and in end-systole (LVESV) was assessed using the Teichholz method according to an established formula [31]: $LVEDV = [7.0 \times (LVIDd)^3]/[2.4 + LVIDd]$ and $LVESV = [7.0 \times (LVIDs)^3]/[2.4 + LVIDs]$. However, stroke volume (SV) was calculated using the formula: $SV = LVEDV - LVESV$. Finally, fractional shortening (FS) was assessed using the formula: $FS\% = [(LVIDd - LVIDs) \times 100]/LVIDd$, and ejection fraction (EF) was assessed using the formula: $EF\% = [(LVEDV - LVESV) \times 100]/LVEDV$ as previously stated [32].

2.5. Statistical Analysis

Data analyses were performed using a commercial statistical software program (SPSS for Windows, version 16.0;