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Research Article

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Comparative Effects of Ciprofloxacin and Levofloxacin on Heart Rate and Qt/Qtcmeasurements in Dogs

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Abstract Fluoroquinolones, despite their use as antibiotics of choice in the treatment of several microbial infections have been associated with the risk of the development of Torsades de pointes (Tdp). This study was conducted to evaluate the comparative effect 2 fluoroquinolone antibiotics, Ciprofloxacin and Levofloxacin, orally administered over a period of 14 days on QT and QTc interval.

In a cross over study, 8 apparently healthy male dogs were equally and randomly divided into 2 groups. Ciprofloxacin and Levofloxacin were orally administered respectively to each group at the dosage of 25mg/kg weight twice daily for a period of 14 days. Electrocardiographic readings were taken 30 minutes before administration and subsequently on days 2, 5, 7, 10 and 14 post-treatment. Lead II QT readings were measured and compared with pre-administration values. For each QT reading, QTc (Bazett) and QTc (Fridericia) values were calculated. Data were analysed using one-way ANOVA with the Tukey post-hoc analysis at a 5% level of significance.

For each of the treatment groups, no significant differences ($p>0.05$) were observed for the heart rate, QT, QTc (Bazett) and QTc (Fridericia) in the dogs when compared with pre-administration values. From this study, neither Ciprofloxacin nor Levofloxacin appeared to have a significant effect on QT and QTc values measured. At the dosage administered, the drugs did not show any observable risk for the manifestation of TdP.

Keywords Ciprofloxacin, Levofloxacin, QT/QTc interval, dogs.

Introduction

Antibacterial agents constitute part of the most extensively used drugs. The potential to influence ventricular repolarization is a very important factor to be considered when these drugs are being used [1]. These valid concerns have arisen from the observation that some commonly used antimicrobial agents have the ability to influence cardiac function in both *in-vitro* models and laboratory animal models [1-3]. Prominent among this class of drugs are the fluoroquinolones which have been widely employed for the treatment of microbial infections, not only in veterinary medicine, but also in human medical practice [4]. The fluoroquinolones exhibit such properties as long elimination half-lives, excellent anti-bacterial activity and spectrum, very good absorption following oral administration and moderate to excellent bio-availability [4-5]. In small animal practice, they have been reported to be very important in the treatment of serious gram-negative infections [6]. Despite these highly beneficial properties in both animal and human medicine, fluoroquinolones have been associated with the prolongation of the QT interval on the electrocardiogram and in effect, the risk of the development of life-threatening polymorphic ventricular arrhythmia,Torsades de pointes (Tdp) [7-8]. After the administration of a drug, an increase in the QT interval is a compelling evidence that the drug may be potentially capable of affecting ventricular repolarization [9]. Drugs that cause Tdp have the potential to block the cardiac voltage-gated potassium channels particularly the rapid component (Ikr) of the delayed rectifier potassium current [10]. On the electrocardiogram (ECG), the QT interval represents the total time taken to achieve the process of ventricular depolarization and repolarization and this process is dependent

on a host of factors which include the ion channels that are involved in cardiac repolarization and the plasma electrolyte concentrations (mainly potassium and calcium) [11-12]. A multiplicity of factors is known to affect the QT interval and they include the length of the cardiac cycle, the activity of the autonomic nervous system, plasma electrolyte concentrations and variations in the ion channels which are responsible for cardiac repolarization [13-14]. This study was conducted to evaluate the comparative effect two fluoroquinolone antibiotics, Ciprofloxacin and Levofloxacin, orally administered over a period of 14 days on QT/QTc interval in dogs.

Materials and Methods

Experimental animals and drug administration

Eight apparently healthy dogs were used in this study. The dogs were obtained from a local dog market in Nigeria and were thereafter housed at the boarding kennels of the Veterinary Teaching Hospital, University of Ibadan. Acclimation to their new environment was done for a period of 14 days prior to the commencement of the study. The dogs were randomly divided into two groups. Each group was treated with either of ciprofloxacin or levofloxacin at the dosage of 25mg/kg weight 12 hourly for a period of 14 days.

Electrocardiographic Recording

Dogs were placed on right lateral recumbency and Lead II ECGs were recorded. The machine was calibrated at 1cm/mV and 50mm/s paper speed. Pre-treatment ECGs were recorded 30 minutes before the administration of the drugs and subsequently on days 2, 5, 7 and 14 of treatment. QT interval was measured from the onset of the QRS complex to the end of the T wave on lead II. Bazett and Fridericia corrections of the QT intervals (QTcB and QTcF respectively) were calculated as follows;

$$QTcB = QT/\sqrt[2]{RR}$$
$$QTcF = QT/\sqrt[3]{RR}$$

Statistical analysis

Data obtained from this study were analysed using one-way ANOVA with the Tukey post-hoc analysis at a 5% level of significance.

Results

Effect on Heart rate

The effects of ciprofloxacin and levofloxacin administration on heart rate is shown in Fig 1. Heart rate in both groups showed a pattern of increment by day two of treatment which was followed by a decrease in value by day 5 of treatment.

Effect on QT, QTc, QTcB and QTcF measurements

QT values in this study are presented in Fig. II. Mean pre-administration QT value was 191.8±4.7ms. This declined through days 2, 5 and 7 to 185.5±7.6ms, 176.3±4.3ms and 173.8±3.9ms respectively. There was a steady increase through days 10 and 14 thereafter to 186.0±4.4ms and 190.0±13.1ms respectively.

QTcB and QTcF values for each of the treatment groups are presented in Figs III and IV respectively. For each of the treatment groups, no significant differences ($p>0.05$) were observed for theQTc (Bazett) and QTc (Fridericia) in the dogs when compared with pre-administration values. Although reductions in the QTcB and QTcF values were recorded for both Ciprofloxacin and Levofloxacin, these increased to near pre-treatment values by the 14th day of treatment.

Discussion

Fluoroquinolones are known to be among the most widely prescribed drugs [15] however despite their usefulness as potent antibiotics, fluoroquinolones havebeen associated with a number of adverse clinical events of which prolongation of the QT segment is very prominent [16] thereby predisposing to the potentially fatal polymorphic ventricular arrhythmia, torsades de pointes [17-19]. This study has given an insight into the comparative effects of both ciprofloxacin and levofloxacin on the electrocardiogram of dogs. By day 2 of treatment, an increase in heart rate was observed in both treatment groups. This was observed to decrease to near baseline values by the 5th day of treatment. The increased heart rate in both groups however fell within the normal range for dogs. Tachycardia has been reported in several species after intravenous administration of the fluoroquinolones. It is however not explicitly clear if this response is related to histamine release or not [20-21].

In a 24-hour study evaluating the comparative effect of three quinolone drugs (Ciprofloxacin, levofloxacin and moxifloxacin) in healthy subjects, the mean QT interval was observed to follow a pattern of initial increase followed by a decrease after several hours [9]. This is similar to the findings in our study which shows a decrease in the QT/QTc values after 48 hours of treatment in both drugs used. In this study, QT/QTc values returned to near pre-treatment values by day 14 of the treatment.

The results obtained from this study showed that there were no significant differences between pre-administration QT/QTc values and those obtained during the course of oral treatment with either ciprofloxacin and levofloxacin for a period of 14 days. An earlier study on quinolone antibiotics including ciprofloxacin and levofloxacin in humans showed that there were no statistically significant diferences in QTc values [22-23] reported only minor QT interval changes after intravenous administration of ciprofloxacin to dogs. The route of administration might have been responsible for the changes observed in the study. Neither ciprofloxacin nor levofloxacin appeared to have any significant effect on QT/QTc values measured in this study. This probably shows the safety of the drugs when orally administered to dogs for a period of 14 days.

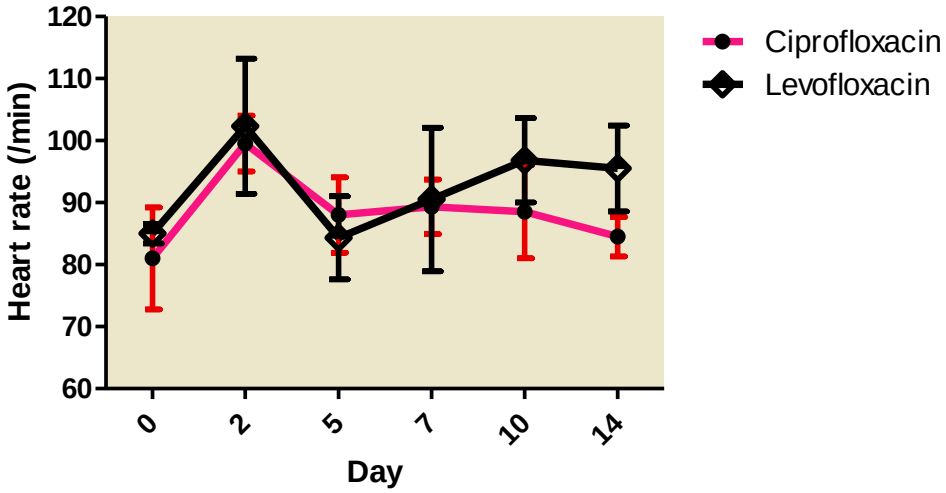

Figure 1: Mean heart rate measurements

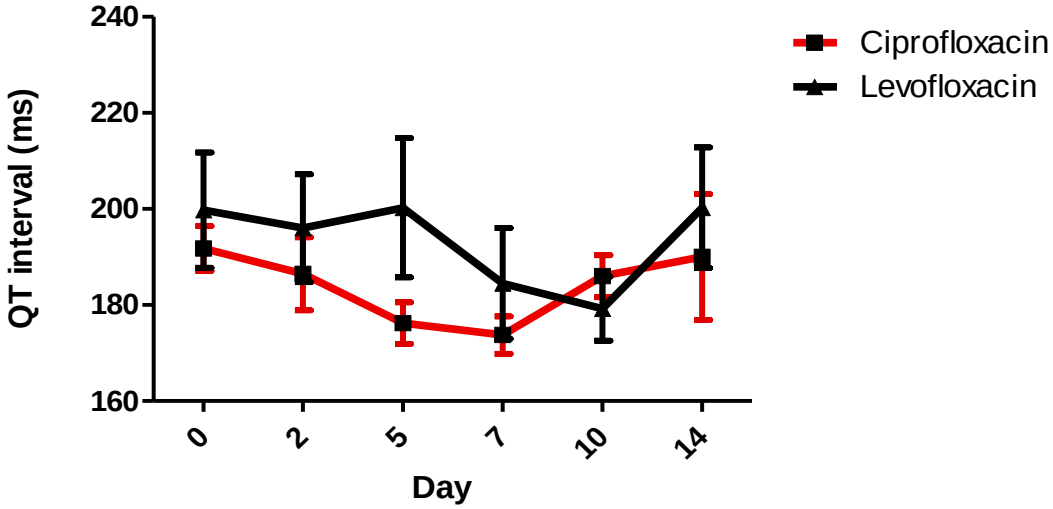

Figure 2: Mean QT interval measurements

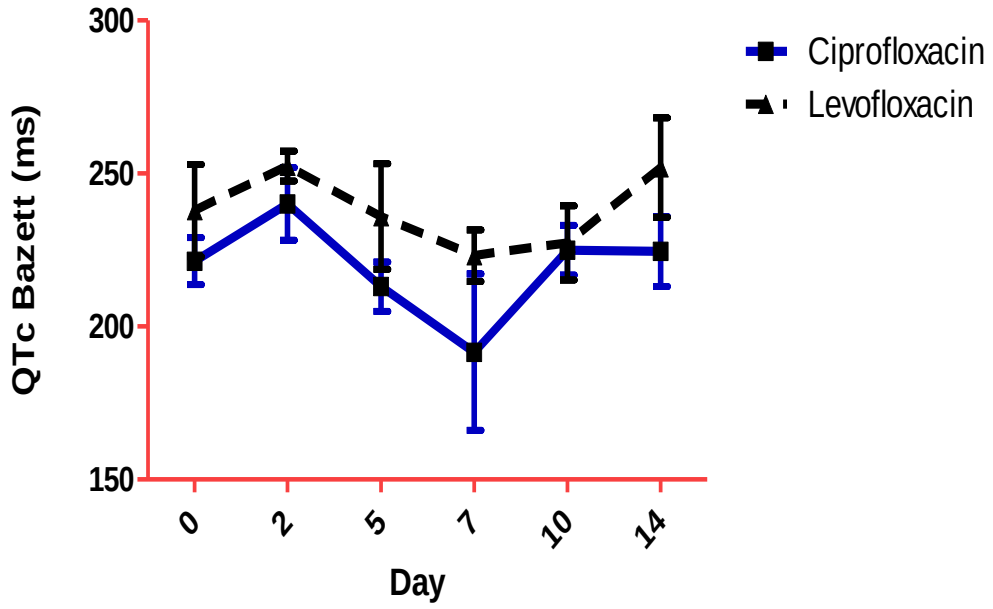

Figure 3: Mean QTcB measurements

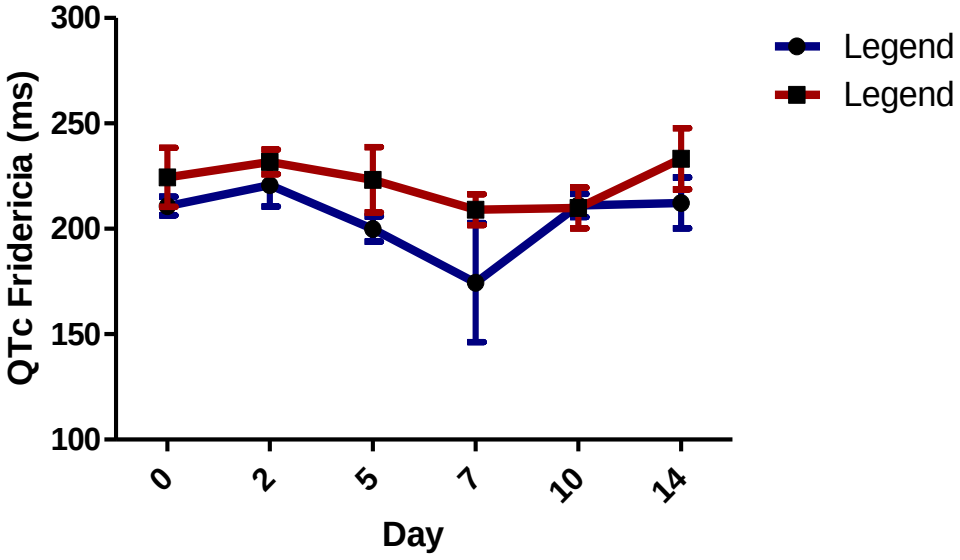

Figure 4: Mean QTcF measurements

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