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EFFECT OF ORALLY ADMINISTERED OFLOXACIN ON LEAD II ELECTROCARDIOGRAM OF DOGS

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ABSTRACT

Introduction: Fluoroquinolones have been employed widely as antibiotic drugs in both human and veterinary medicine owing to their broad spectrum of antibacterial activity and excellent bioavailability. Life threatening arrhythmia has however been associated with the use of some them. This study was designed to study the possible effects of orally administered ofloxacin, a second-generation fluoroquinolone drug on the Lead-II electrocardiogram of dogs. **Materials and Methods:** Twelve Nigerian local dogs aged between 12 and 24 months were used in this study. Ofloxacin was orally administered at the dosage of 20mg/kg body weight daily for a period of 14 days. Lead II electrocardiographic readings were taken and measurements of the heart rate, P-wave duration, P-R interval, R-wave amplitude, QRS complex duration and QT_C values were done. All clinical parameters were taken prior to administration of the drug and subsequently on days 3, 7 and 14 of treatment. **Results:** The major findings were a progressive increase in the heart rate from the day of the first dose to the 14^{th} day and a significant increase in the QTc values through days 3, 7 and 14. Other parameters were however within normal range for dogs. **Conclusion:** This study showed that ofloxacin has a strong potential to cause QT prolongation in the dog, which could trigger the life threatening polymorphic ventricular tachycardia called Torsades de pointes in dogs. Therefore, its use in dogs should be with great caution.

KEYWORDS: Ofloxacin, tachycardia, QT/QTc prolongation.

INTRODUCTION

In the utilisation of antimicrobial drugs, an important factor to consider is the possible effect such drugs may have on ventricular repolarization (Owens, 2001). This is important because many commonly used antimicrobial agents, including the fluoroquinolones have been shown to possess the ability to influence cardiac action potential in both in-vitro and laboratory animal models (Owens, 2001, Ohtani *et al*., 2000, Stahlman and Schwabe, 1997). Since the introduction of the first fluoroquinolone in 1962, several structural modifications has resulted in various products with increased antibacterial properties (Oliphant and Green, 2002). These synthetic antibacterial agents have been extensively used in both human and veterinary medicine with several reported beneficial effects on a wide variety of bacterial diseases of various organ systems (Ihrke *et al*., 1999). They exert their antibacterial effects by inhibiting bacterial DNA gyrase and topoisomerase IV (Bearden and Danziger, 2001). Despite their widely documented beneficial effects, fluoroquinolone antibiotics have the potential to prolong the QT-interval on the electrocardiogram (Falagas *et al*., 2007, Briasoulis *et al.*, 2011) and this carries the risk for the development of the life-threatening polymorphic ventricular tachyarrhythmia, Torsades de pointes (TdP) (Nair *et al*., 2008; Haring and Bauer, 2012). Safety concerns and identified adverse effects including central nervous system effects phototoxicity, hypoglycaemia, thrombocytopaenia, nephritis and haemolytic-uremia syndrome have led to the restriction in the use, or total withdrawal of several fluoroquinolone antibiotics (Ball, 2000; Rubistein, 2001; Zhanel *et al*., 2002; Falagas *et al*., 2007). For example, both sparfloxacin and grepafloxacin were withdrawn from the market because of serious cardiotoxic effects and QTc-interval prolongation (Stahlmann, 2002).

Ofloxacin is a broad spectrum second generation quinolone antibiotic effective against a variety of gram-positive and gram-negative bacteria. It also has been shown to have significant activity against Neisseria gonorrhoeae, Chlamydia trachomatis and Mycobacterium tuberculosis (Smythe and Rybak, 1989).

This study was designed to investigate the effect of orally administered ofloxacin, a second-generation fluoroquinolone, on the canine lead- II electrocardiogram.

MATERIALS AND METHODS

Twelve Nigerian local dogs aged between 12 and 24 months were used in this study. Ofloxacin was orally

administered at the dosage of 20mg/kg body weight daily for a period of 14 days. Lead II electrocardiographic readings were taken and measurements of the heart rate, P-wave duration, P-R interval, R-wave amplitude, QRS complex duration and QT_C values were done. All clinical parameters were taken prior to administration of the drug and subsequently on days 3, 7 and 14 of treatment.

RESULTS

Results for the heart rate, P-R interval, QRS complex duration, R-wave amplitude, QT-interval as well as the Bazett's correction of the QT-interval are shown in figures 1, 2, 3, 4, 5 and 6 respectively. There was a significant ($p<0.05$) increase in the mean heart rate by day 3 of treatment. This increase continued up till day 14 of treatment (Fig 1). A significant ($p<0.05$) and progressive reduction in the mean PR-interval was observed through days 3, 7 and 14 (Fig 2). In a similar manner, significant ($p<0.05$) increase in the mean QRS complex duration was observed on day 3 of treatment. This increased to a maximum value of 64.4±5.4 ms on day 7 of treatment. A slight decrease to 60.7±2.2 ms was observed by day 14 of treatment. A significant ($p<0.05$) reduction in the R-wave amplitude to was observed by day 3 of treatment. This however increased to 1.22±0.15 mV and 1.24±0.16 mV by days 7 and 14 respectively. There was a significant ($p<0.05$) increase in the QT segment by day 7 of treatment to 235.0±7.5 ms. This decreased to 185.4±3.1 ms by day 7 of treatment. A significant increase in the Bazett's correction of the QT-interval was observed from day 3 of treatment. This further increased by day 7 of treatment to 365.1±24.5 ms and thereafter decreased slightly to 334.3±8.0 by day 14.

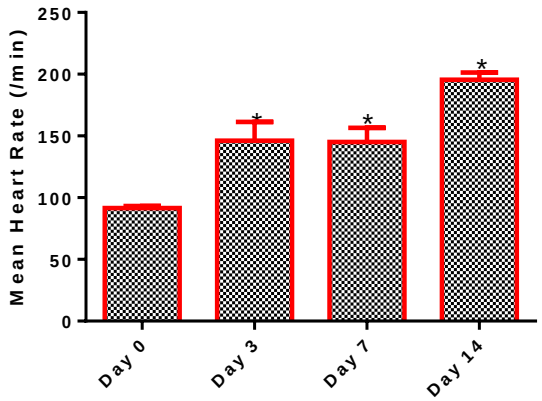

Fig. 1 Effect of Ofloxacin treatment on Heart rate

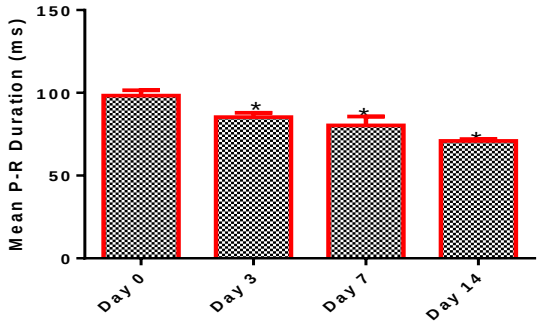

Fig. 2 Effect of Ofloxacin treatment on PR interval

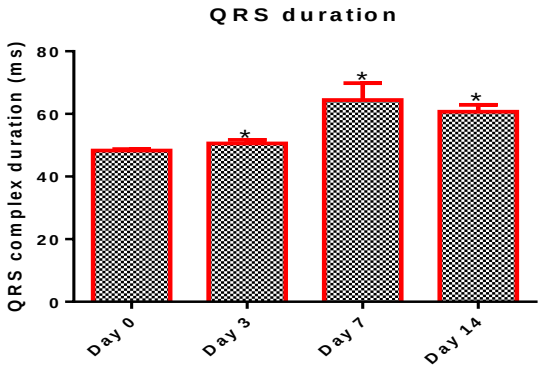

Fig: 3. Effect of Ofloxacin treatment on QRS duration

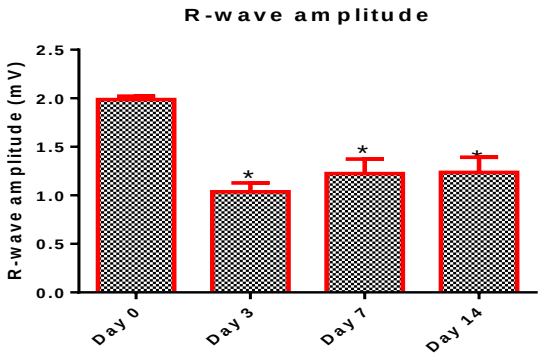

Fig. 4 Effect of Ofloxacin treatment on R-wave amplitude

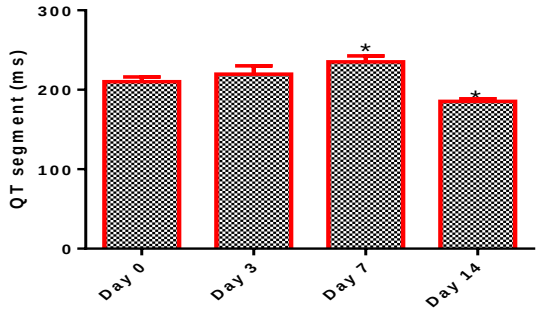

Fig. 5 Effect of Ofloxacin treatment on QT interval

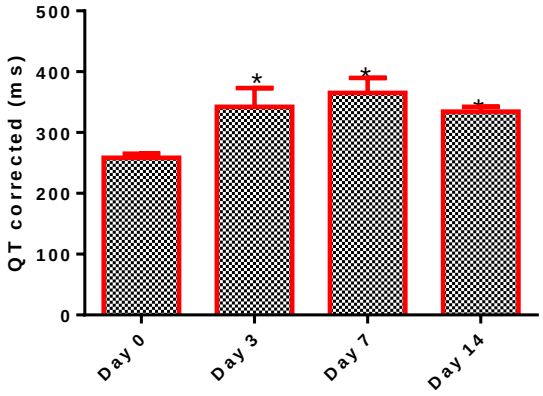

Fig. 6 Effect of Ofloxacin treatment on QTc (Bazett)

DISCUSSION

This study gives an insight into the effect of orally administered ofloxacin on the lead-II electrocardiogram of dogs. Administration of ofloxacin led to a statistically significant increase in heart rate of dogs. By the 14th day of treatment, the heart rate had risen from the pre-administration value of 91.6±1.6 /min to 195.6±5.7 /min. Syncope and tachycardia have been reports as adverse reactions following treatment with ofloxacin (Aronson, 2009). Similarly, an increase in heart rate has also been reported with levofloxacin treatment (Basyigit *et al*., 2005; Omobowale *et al*., 2016). In this study, the heart rate had risen by more than 100% by the 14th day of therapy.

Although statistically significant differences were observed between pre-administration values of the PR-interval, QRS duration and R-amplitude and those recorded on days 3, 7 and 14, (Figs 2,3 and 4), these values were within normal limits for dogs. The effects observed on the PR interval, The P-R interval was observed to be significantly ($p<0.05$) reduced in this study from day 3 of treatment. This probably points to the ability of ofloxacin to cause a reduction in the atrioventricular conduction time. In contrast, Ghaffari and Parsamehr, (2009) had reported that ciprofloxacin, a commonly administered quinolone did not show any effect on PR-interval in dogs. The reason for the progressive shortening in our study in however not known.

Quinolones have been associated with an increase in the QT-interval, a phenomenon which can lead to the potentially fatal ventricular arrhythmia, TdP (Nair *et al*., 2008; Haring and Bauer, 2012). In this study, the administration of ofloxacin caused a significant ($p<0.05$) increase in QT interval on days 7 and 14 of treatment. Drugs which have the potential to cause TdP are potentially capable of blocking the cardiac voltage-gated potassium channels particularly the rapid component (Ikr) of the delayed rectifier potassium current (Fenichel *et al*., 2006). In humans, the administration of Ofloxacin has been associated with TdP (Frothingham, 2001) however, it has not been shown to prolong QT interval in rabbits (Adamantidis *et al*., 1998). Because of the adverse effects of tachycardia and prolonged QT interval found in this study, the use of Ofloxacin in dogs should be with great caution because of the potential to cause TdP.

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