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Original article

Influence of long-term oral application of quinolones on the ECG curve in dogs

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Abstract

The aim of the study was to analyse the influence of enrofloxacin and pradofloxacin administered orally for 14 days on the ECG in dogs. The ECG was performed before and after a 14 day period of quinolone administration. There was an increase in the QTc and the TpTe interval in the group treated with quinolones. QTc was prolonged by 24 ms (p=0.001). The TpTe interval was shortened, on average, by 6.55 ms (p=0.048). In the group treated with enrofloxacin, QTc was prolonged by 16.27 ms (p=0.006) and the TpTe interval was shortened by 9.64 ms (p=0.050), the TpTe/QT index was reduced by 0.034 (p=0.050) on average. In dogs treated with pradofloxacin, QTc was prolonged by 21.55 ms (p=0.012) on average. The results suggest that a prolonged administration of quinolones can increase the risk of arrhythmias. Furthermore, different generations of these drugs increase this risk to various degrees. The study proved that second generation quinolones, such as enrofloxacin, significantly change the phase of depolarization and repolarization of the ventricles, at the same time increasing the risk of ventricular arrythmia. Pradofloxacin does not change the TpTe and TpTe/QT values, so it is safer in use.

Key words: dog, enrofloxacin, pradofloxacin, ECG curve

Introduction

Quinolones are chemotherapeutics with bactericidal effects. They are widely applied both in human and veterinary medicine. Enrofloxacin and ciprofloxacin are second generation fluoroquinolones, while the new and most commonly used pradofloxacin is a third generation fluoroquinolone. 10-40% of enrofloxacin is metabolised into ciprofloxacin in the liver (Barbhaiya et al. 2013). Numerous studies in humans have proved that quinolones influence the prolongation of the depolarization and repolarization of the heart ventricles (Sheridan 2000, Devlin et al. 2013). This process is influenced by many factors, such as the function of the autonomic nervous system, the heart rate, the age, the sex, the concentration of electrolytes in the blood serum and the function of ion canals present in cardiomyocytes (Lubiński et al. 1998, Sheridan 2000). The depolarization and repolarization time of the heart ventricles adjusted by the heart rate is related to the QTc interval on the ECG curve. Quinolones influence the prolongation of QTc by blocking potassium channels, i.e. the rapidly activating channel of a delayed potassium rectifier current – I_{Kr}

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(Antzelevitch 2004). The mechanism is the same both in people and in dogs (Wang et al. 2003). It was proved that, in people, the significant prolongation of QTc may lead to life-threatening ventricular arrhythmia, such as Torsades de Pointes (TdP) (Lubiński et al. 1998, Letsas et al. 2010). Apart from the prolongation of the QTc, there are several other indicators of the arrhythmogenic effect of quinolones on the ventricles, such as the Tpeak Tend (TpTe) interval and TpTe/QT index (Boothe et al. 2001, Shimizu et al. 2002, Chiang 2006, Antzelevitch 2008).

There are few reports in veterinary medicine concerning the influence of quinolones on the ECG curve parameters in dogs (Frothingham 2001, Toyoshima et al. 2005, Castro et al. 2006, Piccirillo et al. 2012). To date, studies have assessed the influence of ciprofloxacin, marbofloxacin and enrofloxacin applied subcutaneously, intravenously and orally. The influence of pradofloxacin has not yet been tested.

The aim of the study was to analyse the influence of enrofloxacin and pradofloxacin administered orally for 14 days on the ECG curve in dogs.

Materials and Methods

20 dogs of various breeds, sexes and age that were patients of the Department of Internal Medicine and Clinic of Horses, Dogs and Cats, Wroclaw University of Environmental and Life Sciences were included in the study. The average age of the dogs was 6 years (range from 2 to 11 years) and the average weight was 15.5 kg (range from 7 to 34 kg). There were six females and 14 males. All the dogs were treated with quinolones for superficial pyoderma. They underwent a detailed clinical examination to exclude any accompanying diseases. The ECG examination was preceded by a complete blood count (Micros ABX Vet) and serum biochemistry, where the levels of ALT and AST, urea, creatinine, glucose, cholesterol, sodium (Na+), chloride (Cl-), potassium (K+) were assessed using the Konelab Prime 30ISE device. Thyroxine and free thyroxine were also measured by enzyme-linked fluorescence assay (ELFA) method. An echocardiogram and ECG were carried out to exclude the presence of cardiovascular diseases and conduction disorders.

The studied dogs were divided into two groups depending on the administered substance. The first group consisted of 10 dogs, which received enrofloxacin orally at 10 mg/kg body weight once a day for at least two weeks. The second group consisted of 10 dogs that were administered pradofloxacin orally at 3-4.5 mg/kg body weight once a day for at least two weeks. The ECG examination was carried out in right lateral recumbency prior to quinolone administration, and again on the 14th day of its administration. Limb (I, II, III, aVR, aVL, aVF) and precordial leads (V1, V2, V4) were used. The heart rate, RR interval, the width of the P wave and of the QRS, PQ, QTc and QRS axes were measured on the ECG curves. The QT interval was adjusted using the Fridericia formula (Fridericia 1920). Next, the polarisation of the T wave, the TpTe interval measured from the peak to the end of the T wave and the TpTe/QT index were assessed.

The Wilcoxon signed rank test was used for statistical analysis. The significance level was set at $p<0.05$.

According to the Polish law, the consent of the Ethics Committee is required for procedures more invasive than a needle injection (blood sampling). Blood sampling was carried out to evaluate the dermatological status of the patient. The oral consent for the blood sampling, electrocardiography and echocardiography was obtained from all the owners.

Results

The internal temperature, heart rate and respiratory rate were within the reference values, CRT was <3 seconds and the mucous membranes were pink in all the dogs. Skin lesions typical of superficial pyoderma were visible in all the animals. All the laboratory parameters (Table 1 and 2), as well as the electrocardiographic and echocardiographic indices of all the dogs, remained within the respective reference limits. The ECG parameters obtained are presented in Table 3. The results of the study showed a statistically significant increase in the QTc and the TpTe interval in the whole group treated with quinolones. QTc was prolonged, on average, by 24 ms ($p=0.001$) and the TpTe interval was shortened, on average, by 6.55 ms ($p=0.048$). The polarization change of the T was observed in seven dogs (35%), five of which were from the enrofloxacin group (50%) and two were from the group treated with pradofloxacin. In the group receiving enrofloxacin, QTc was prolonged, on average, by 16.27 ms ($p=0.006$) and the TpTe interval was shortened by 9.64 ms ($p=0.050$). In that group, the TpTe/QT index underwent statistically significant changes as it was reduced on average by 0.034 ($p=0.050$). In the group treated with pradofloxacin, QTc was prolonged, on average, by 21.55 ms ($p=0.012$). The remaining ECG parameters did not undergo statistically significant changes. No arrhythmia was observed in any of the dogs.

Table 1. Blood morphology parametrers.

Parameter	Group 1, n=10	Group 2, n=10
WBC [G/l]	9.82 (± SD 3.0)	11.13 (± SD 4.2)
RBC [T/l]	6.85 (± SD 0.6)	6.61 (± SD 0.6)
HGB [mmol/l]	9.43 (± SD 1.4)	8.76 (± SD 1.3)
HCT [l/l]	0.49 (± SD 0.04)	0.46 (± SD 0.04)
PLT [G/l]	316.3 (± SD 72.9)	332.9 (± SD 69.2)
MCV [fl]	73.2 (± SD 3.6)	71.4 (± SD 1.9)
MCH [fmol]	1.46 (± SD 0.07)	1.4 (± SD 0.05)
MCHC [mmol/l]	19.9 (± SD 0.3)	19.78 (± SD 0.3)
LYM [G/l]	1.01 (± SD 0.4)	1.01 (± SD 0.3)
MON [G/l]	0.35 (± SD 0.1)	0.45 (± SD 0.1)
GRA [G/l]	8.46 (± SD 2.7)	9.67 (± SD 3.8)

Table 2. Biochemical blood parameters.

Parameter	Group 1, n=10	Group 2, n=10
ALT [U/l]	44.5 (± SD 13.6)	51.9 (± SD 9.7)
AST [U/l]	61.3 (± SD 8.4)	68,2 (± SD 6.4)
Creatinine [µmol/l]	105.1 (± SD 14.8)	95 (± SD 8.3)
Urea [mmol/l]	5.7 (± SD 2.5)	4,3 (± SD 1.1)
Glucose	4.2 (± SD 0.7)	4.7 (± SD 0.9)
Na+ [mmol/l]	147.1 (± SD 0.4)	149.4 (± SD 1.1)
Cl- [mmol/l]	110.7 (± SD 3.9)	105.6 (± SD 4.7)
K+ [mmol/l]	4.5 (± SD 1.3)	4.6 (± SD 0.9)
Cholesterol [mg/dl]	237.2 (± SD 20.7)	187 (± SD 27.1)
T4 [nmol/l]	31.9 (± SD 14.6)	28.6 (± SD 7.9)
fT4 [pmol/l]	12.54 (± SD 4.1)	10.97 (± SD 2.3)

Table 3. Electrographic values of the QTc, TpTe and TpTe/QT in dogs treated with enrofloxacin and pradofloxacin.

Group	QTc (ms)			TpTe (ms)			TpTe/QT		
	day 0	day 14	p value	day 0	day 14	p value	day 0	day 14	p value
Enrofloxacin, n=10	259.82 (±SD 14.13)	276.09 (±SD 19.67)	p=0.006*	50.54 (±SD 17.41)	40.91 (±SD 12.91)	p=0.050*	0.228 (±SD 0.075)	0.194 (±SD 0.067)	p=0.050*
Pradofloxacin, n=10	272.55 (±SD 25.88)	294.11 (±SD 31.79)	p=0.012*	42.83 (±SD 12.10)	37.50 (±SD 10.79)	p=0.656	0.202 (±SD 0.050)	0.177 (±SD 0.040)	p=0.858
Total, n=20	270.54 (±SD 23.75)	294.54 (±SD 28.65)	p=0.001*	44.00 (±SD 11.97)	37.45 (±SD 11.32)	p=0.048*	0.212 (±SD 0.064)	0.185 (±SD 0.053)	p=0.065

* – statistically significant, QTc – corrected QT interval, TpTe – duration of early and late repolarizations, ms – miliseconds

Discussion

In humans, drug-dependent prolongation of the QT interval was first examined over 30 years ago (Roden et al. 1986, Kallergis et al. 2012). In his retrospective study, Frothingham (2001) defined the frequency of the TdP type arrhythmia following quinolone application in the USA from 1996 to 2001. He noted 25 such episodes (two after the administration of ciprofloxacin and ofloxacin, eight following gatifloxacin administration and 13 after levofloxacin administration). The studies proved that the greatest risk of this type of tachycardia is related to gatifloxacin (27 cases in 10 million prescriptions) and levofloxacin (5.4/10 million), while ciprofloxacin proved to be much safer (0.3/10 million) (Friedman et al. 2003). Studies on humans found that some drugs can evoke effects similar to the ones caused by a mutated HERG gene on chromosome 7, which codes an improper K+ channel protein, which blocks the potential-dependent potassium channel (Vormberge et al 2006). In veterinary medicine, there are many chemotherapeutic drugs from the quinolone group that prolong QTc.

The phenomenon of post-medication QTc prolongation is mainly related to the inhibition of the rapidly activated delayed potassium rectifier current (I_{Kr}), which results in the elongation of the repolarization period, i.e. the third phase of the action potential (Yang and Roden 1996). The increase in the heart muscle effective refraction period, the presence of early afterdepolarizations (EADs) and the re-entry phenomenon are the results of its prolongation. The medication-induced TdP type polymorphic tachycardia is caused by EADs where the balance between the repolarization and depolarization time is disrupted in the third phase of the action potential. The EADs may then lead to the presence of an evoked response of the action potential and, in effect, to tachycardia.

In our study, we found statistically significant lengthening of the QT interval after a 14-day administration of enrofloxacin and pradofloxacin using doses recommended by the manufacturers. Previous studies carried out on dogs, aimed at assessing the influence of some quinolones on the ECG curve (Frothingham 2001, Toyoshima et al. 2005 Castro et al. 2006, Piccirillo et al. 2012). The longest study lasted five days (Piccirillo et al. 2012). To date, there have been no studies assessing the effects of pradofloxacin and long-term administration of other quinolones in dogs. The majority of the previous studies aimed at examining the influence of a single dose administration of the drug measured in a short period of time. Toyoshima et al. (2005) proved that an oral administration of ciprofloxacin at a dose of 5-200 mg/kg during 24 hours does not cause significant changes in the QT interval. That study was carried out on four dogs and the drug was administered once (Toyoshima et al. 2005). Other studies carried out by Ghaffari and Parsamehr (2009) on ciprofloxacin administered intravenously during 15 minutes at a dose of 10 mg/kg showed the lengthening of the QT interval by 20 ms in the 60th minute following the drug injection. However, the authors explain this change by the decrease in the frequency of the rhythm, and not the impact of the drug itself (Frothingham 2001). The authors did not calculate the QTc interval. Quinolones were administered for the longest period of time in the study by Agudelo-Ramirez et al. (2012). In their study on dogs, they administered enrofloxacin twice a day subcutaneously at a dose of 5 mg/kg and carried out daily ECG examinations. The examinations did not show any significant change in the QT and the QTc intervals. However, enrofloxacin was administered at a dose three times lower than that recommended by the producer for skin infections or lower airway infections.

In the available literature, none of the authors determined the changes in the TpTe interval and the TpTe/QT index following quinolone administration in humans or dogs. These parameters are the newest ECG parameters used to determine the risk of ventricular arrhythmia (Boothe et al 2001, Shimizu et al. 2002, Chiang 2006, Antzelevitch 2008). The TpTe interval is an index of transmural dispersion of repolarization. The transmural dispersion of repolarization is caused by the differences in the action potential between the three myocardial layers (epicardial, M cell and endocardial) (Liu et al. 2006). Top value of positive T wave (Tpeak) indicates the suppression of the repolarization of the epicardial cells, while the end of the T wave (Tend) presents the end of repolarization in the M cells. M cells have the longest time of transmural dispersion of repolarization and are much more sensitive to I_{Kr} channels blocks caused by drug-induced lengthening of QT than the cells of the remaining layers. Therefore, we can observe a significant lengthening of this potential in the M cell layer without significant changes in the action potential in other layers. This leads to a notable increase of the transmural dispersion of repolarization (Antzelevitch 2004, Chanoit et al. 2005, Agudelo-Ramirez et al 2012). TpTe/QT index is an even more sensitive indicator of the risk of arrhythmia as it eliminates the effect of distorting factors, such as the heart rhythm and the QT interval (Ghaffari and Parsamehr 2009).

In the group of dogs treated with enrofloxacin, QTc, TpTe and TpTe/QT underwent statistically significant changes compared to the dogs treated with pradofloxacin, where only QTc changed significantly. These results suggest that a prolonged quinolone administration can increase the risk of arrhythmia. Dif-

ferent generations of these drugs increase the risk to various degrees. This study also found that enrofloxacin, which is a second generation drug, significantly changes the phases of depolarisation and repolarization of the ventricles, while increasing the risk of ventricular rhythm distortions. Despite the fact that pradofloxacin significantly lengthens the QT interval, it does not change the TpTe and TpTe/QT values. Hence, it is safer to use.

Both TpTe and QT are widely used in human medicine to assess the risk of ventricular arrhythmia. There are studies showing that in people with an acquired long QT syndrome, the TpTe parameter is more effective than QTc in assessing the risk of TdP (Shimizu et al. 2002). In another study, Xian-ming et al. (2013) proved that the TpTe/QT index could assess the risk of ventricular arrhythmias and sudden cardiac death in people with cardiovascular disease. Barbhaiya et al. (2013) concluded that both parameters are very useful in assessing the risk of ventricular arrhythmias in patients who underwent resynchronising therapy (Antzelevitch 2008). There are also studies proving the usefulness of these parameters in patients with the Burgada syndrome (Kay et al. 1983, Braschi et al. 2011). In veterinary medicine, there are isolated reports of the use of these markers and further studies are necessary to confirm their usefulness (Moss 1999).

Conclusion

The results indicate that quinolones in dogs can cause lengthening of QTc. It would be beneficial to conduct an observation on a larger group of dogs. Hence, patients should be monitored using ECG during long-term administration of quinolones.

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