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Evaluation of the Mexiletine Effects on Normal Cats' Electrocardiogram

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Abstract

Mexiletine has been suggested in various studies for the treatment of ventricular arrhythmias. Extremely low toxicity of this drug has been reported in these literatures; however, there is no reasonable report on the effects and function of this drug on the cat's heart processes in different phases of cardiac contraction. This article evaluated the effects of different dosages of mexiletine on cat's electrocardiography.

Seven cats were used for this study and incremental dosage method with oral capsule has been used. Before starting the study, each cat were evaluated by an electrocardiogram sample, which was considered as a normal electrocardiogram) ECG(. To evaluate the effects of mexiletine, doses of 4, 10, 15, 20 and 40 mg/kg were adjusted and prescribed. For each cat, the doses were prescribed sequentially every 24 hours and after prescription of the drug, the cats were examined clinically and electrocardiographically. This evaluation was done at the peak of the drug, about 2 hours after prescription. Finally, all clinical observations and ECGs were evaluated.

In the clinical study, any clinic symptoms was considered and rhythm, heart rate, and determination of heart electrical functions such as P amplitude and duration, QRS duration, R amplitude, ventricular contraction time (QT interval) and PR interval were evaluated in electrocardiographic experiments.

According to the results of this study, it can be concluded that the drug is quite safe for cats and no cardiac complication and electrophysiological disorder was observed even with the use of high doses or even incremental doses, so this indicates that the drug can be safe in terms of cardiac effects.

Key words: *mexiletine, electrocardiography, cats, small animal, veterinary,*

Introduction

Heart diseases are one of the most common and important diseases in human being and animals, especially dogs and cats. Among heart diseases, heart arrhythmias are assigned as a special and common group, almost [1, 2]. Heart arrhythmias may generate by different origins and can produced from sino-atrial node, atrial-ventricular node and even due to electrolytes disorders. In some guidelines, treatments based on medical advices are not appropriate for animals because of a different understanding of the fundamental alterations (such as coronary heart disease versus non-coronary heart disease). Unfortunately, vet- clinicians do not know what is happening in dogs and cats with arrhythmia for various reasons and it is not possible to compare arrhythmia with different causes regardless of the outcome and the medication results [1, 2].

Various classes of medications are available and used to treat cardiac arrhythmias. Antiarrhythmic drugs are mainly divided into four categories, given their potential effects on action potential. For example, selective drugs in group I, block fast sodium channels and reduce sodium inversion during the 0-depolarization step. This group is divided into 3 subgroups A, B and C with different drugs in these categories [3, 4].

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Due to the effects of the antiarrhythmic drug class I_B which blocks the fast sodium channel in the heart, the drug group therefore affects the zero-phase of cardiac contraction and has beneficial effects on ventricular tachy-arrhythmias. Given the performance of this class of drugs at stage zero of cardiac contraction, minimal pharmacological effects can be observed in the sinoatrial node, atrial and ventricular nodes and atrial muscles [5].

Mexiletine is one of the drugs recently proposed for veterinary use, which is an oral analogue of lidocaine. It appears to be more effective and healthier than lidocaine. Mexiletine, which belongs to group I_B, blocks fast sodium channels and has been suggested in various sources for the treatment of ventricular arrhythmias [6, 7].

Mexiletine is orally absorbed and less than 10% of this drug eliminated by the first passage of the liver. Side effects vary in dogs and include nausea, anorexia and tremor. Sinus tachycardia, imbalances, confusion and thrombocytopenia are other potential problems [1]. No information is available on its use in cats [1], but in some cases it has been used to treat dogs.

For example, in a group of dogs of the Boxer breed with familial arrhythmia, mexiletine continuously tested with atenolol as one of four forms of treatment. This anti-arrhythmia treatment has been shown to decrease the frequency and degree of ventricular arrhythmia, as well as a decrease in the peak heart rate. However, the frequency of syncope has not decreased with this understanding of treatment or other methods studied. Both Mexiletine and Tocainide have synergistic properties in combination with drugs of class IA and II. These drugs are mainly used to treat ventricular arrhythmias and cardiac glycoside poisoning arrhythmias (lidocaine, Phenytoin). Tocainide is a closely related lidocaine (1, 2, 8-12).

According to the available literature and sources, no comprehensive study of the function of this drug has been evaluated in cats (2). This study, performed on 7 healthy and adult cats, studied the effects of Mexiletine on the cardiac electrophysiology of cats.

Materials and Method

Seven cats were used for this study. The cats selected were all healthy and stray. They were all short haired cats and tried to be selected from a weight class. The selected cats were also of different ages (1-3 years) and sex. All of the selected cats were clinically healthy and none showed cardiac disease at the time of examination. In addition to clinical examinations and blood tests, cardiac function was evaluated by electrocardiography to assess cardiac health in these cats.

The cats adapted to the new environment before the study and used the same commercial food during the study. The studied cats were repeatedly placed on the same examination table and trained to adapt to the environment and how to place the electrocardiogram. After adjustment with the examination table, only physical restraint was applied for electrocardiography to minimize stress at studied time.

Hexagonal electrocardiogram was obtained by Siemens single channel electrocardiography in each cat and selected as primary and control electrocardiogram.

The ECG obtained from cats at the first time (no-prescription conditions) was introduced as zero-dose (D0) and control ECG. Mexiletine is available as a 100 mg oral capsule. The drug was administered daily to 7 cats for 10 days to evaluate the drug's effects. The doses used in this study were 4, 10, 15, 20 and 40 mg / kg. Capsules were administered orally (daily) and electrocardiograms were taken at least two hours after drug prescription in the time of drug peak effect. After 10 days of prescription of mexiletine, the cats were in rest for two weeks as drug wash out time and then, higher doses were administered to the same cats.

At the time of drug prescription, if any neurological symptoms (incoordination, ataxia, etc.) as well as gastrointestinal symptoms (vomiting and diarrhea) were observed, all cases were recorded and images and videos were obtained. Finally, in electrocardiographic examination, heart rhythm, heart rate and cardiac coordinates including P amplitude and duration, QRS duration, R amplitude, QT and PR interval were investigated. Finally, evaluation of results in this study was adjusted to mean ± SE, and the evaluation list of the results of different doses was analyzed by one-way ANOVA followed by Tukey test.

Results

All results have been evaluated for lead 2 standardization in this lead and it should be noted that no apparent abnormality was observed in any ECG and all ECGs were without arrhythmia.

In evaluating the P wave amplitude in the normal state and after administering the drug at different doses, the same results as detected in table 1 (A) were observed. According to the results, it appears that this drug has no positive or negative effect on P wave amplitude. In cats, the Pamp should not exceed 0.2 mV.

Table 1. P wave amplitude in (mV) (A), P wave duration (B), R wave amplitude (C), QRS duration (D), PR interval (E), QT interval (F) (per second) and the number of heartbeats (in minute) in cats.

		Before prescription of drug	Dose 4 mg/kg	Dose 10 mg /kg	Dose 15 mg/kg	Dose 20 mg/kg	Dose 40 mg/kg
A	P wave amplitude (Mean ± SE)	0.114±0.009	0.107±0.007	0.107±0.007	0.107±0.007	0.114±0.009	0.142±0.013
B	P wave duration (Mean ± SE)	0.024±0.002	0.024±0.002	0.025±0.002	0.025±0.002	0.022±0.002	0.028±0.002
C	R wave amplitude (Mean ± SE)	0.63±0.098	0.74±0.065	0.60±0.058	0.62±0.074	0.67±0.032	0.60±0.072
D	QRS wave duration (Mean ± SE)	0.028±0.002	0.031±0.002	0.032±0.002	0.028±0.003	0.032±0.003	0.035±0.002
E	PR int duration (Mean ± SE)	0.067±0.004	0.068±0.005	0.070±0.002	0.068±0.002	0.057±0.003	0.061±0.003
F	QT int duration (Mean ± SE)	0.128±0.001	0.147±0.007	0.145±0.006	0.132±0.004	0.131±0.007	0.137±0.009
G	Number of heartbeats (Mean ± SE)	220±23.62	206±15.91	209±12.26	209±16.74	199±23.63	184±17.98

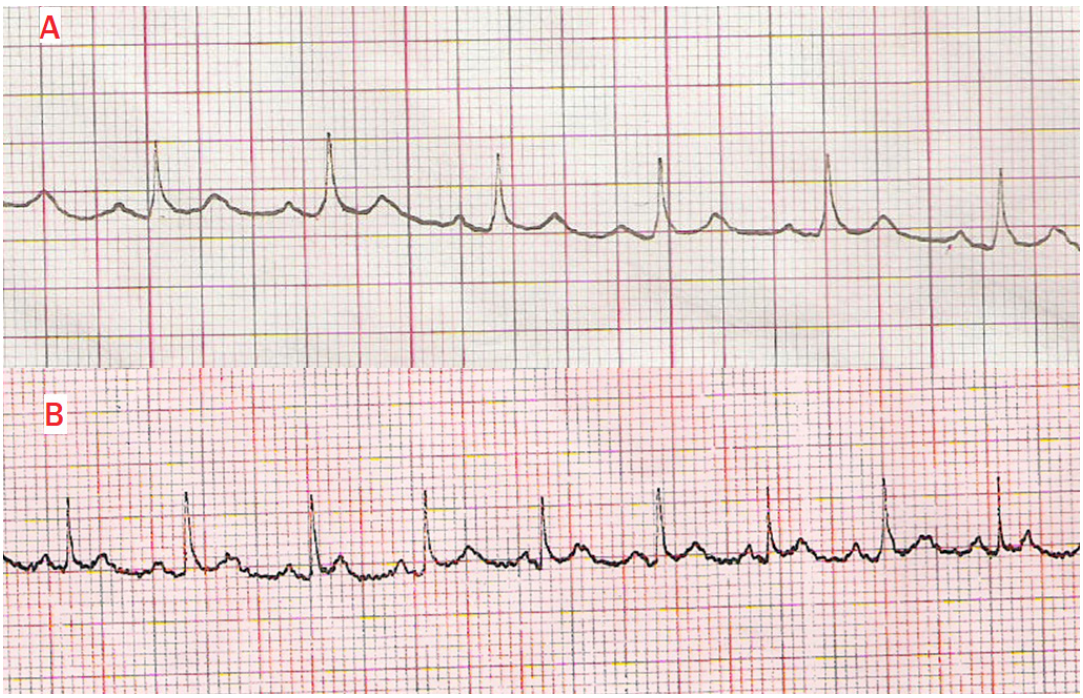

Figure 1. Normal ECG of one cat (50 mm/s, 1 mv) (A), and ECG of the same cat after prescription of the drug at a dose15 mg / kg (50 mm/s,1 mv) (B).

The same results were observed in the P duration evaluation after the administration of drugs at different doses, as shown in table 1 (B). According to the results, it seems that this drug does not have a significant effect on P wave duration. In normal cats, the normal P duration is less than 0.04 seconds.

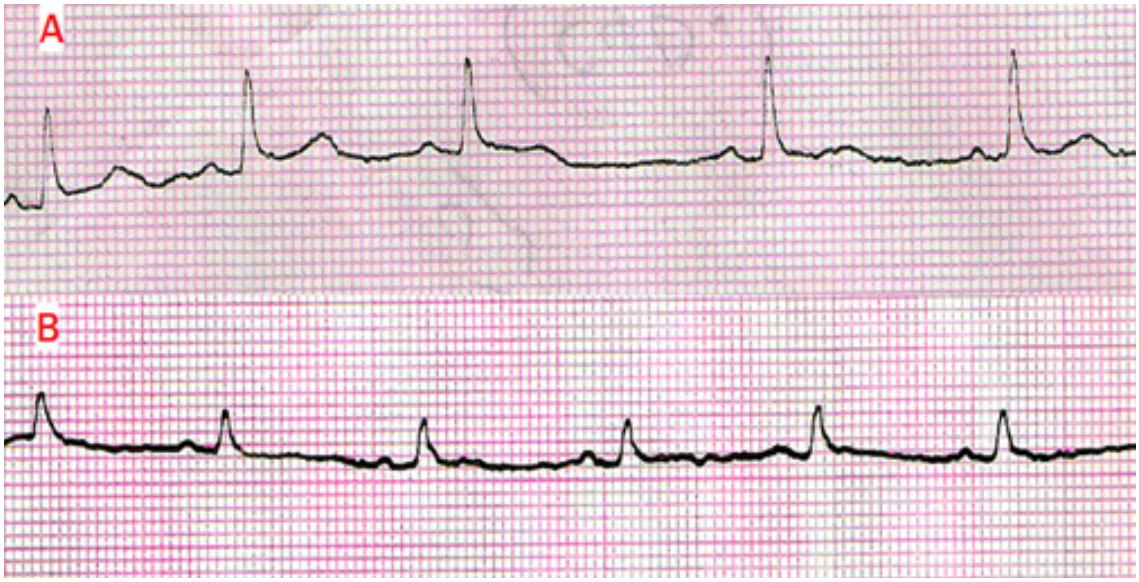

Figure 2. Normal ECG of one cats (50 mm/s, 1 mv) (A), and ECG of the same cat after prescription of mexiletine at a dose 20 mg / kg (50 mm/s, 1 mv (B).

The following results regarding the R wave amplitude obtained before and after drug administration suggest that different doses have no significant effects on the R wave amplitude. However, in some cases, some decrease in the amplitude of the R wave is observed. The amplitude of R wave varies in different references but should not be less than 0.5 mV. However, in this study, the amplitude of the R wave decreases at some doses (table 1 (C)).

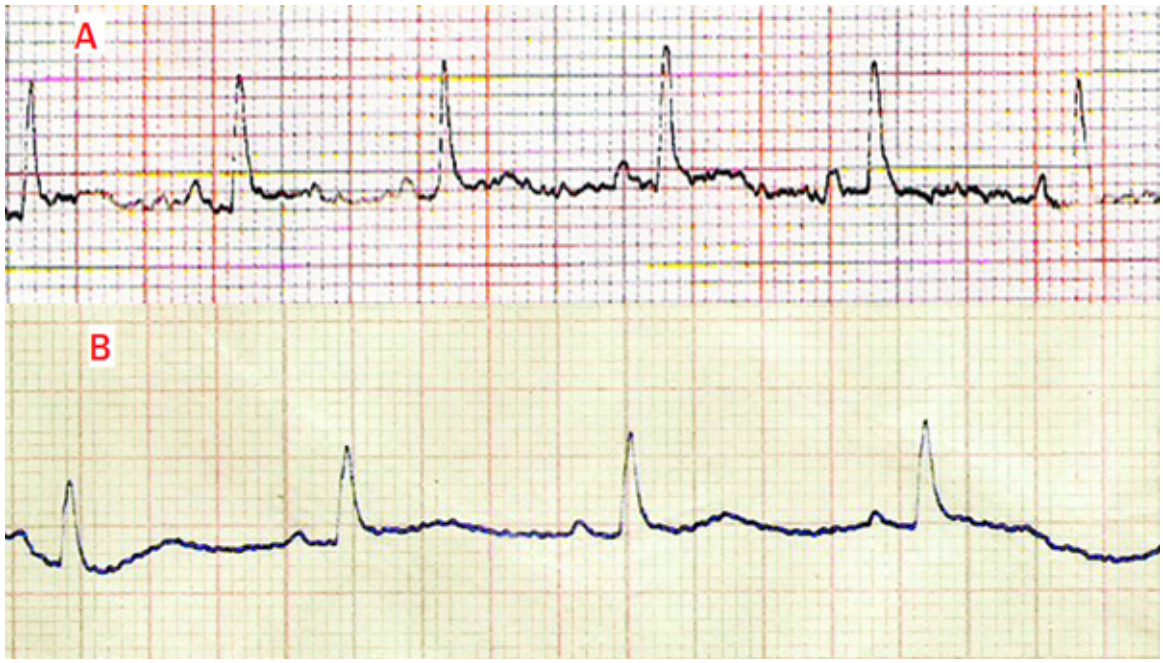

Figure 3. ECG of one cat under study (50 mm/s, 1 mv) (A), and ECG of the same cat after prescription of the drug at a dose 20 mg / kg (50 mm/s, 1 mv).

There appears to be little difference in the QRS duration with different drug doses as shown in table 1 (D). It should be noted that the QRS duration should be less than 0.04 in cats.

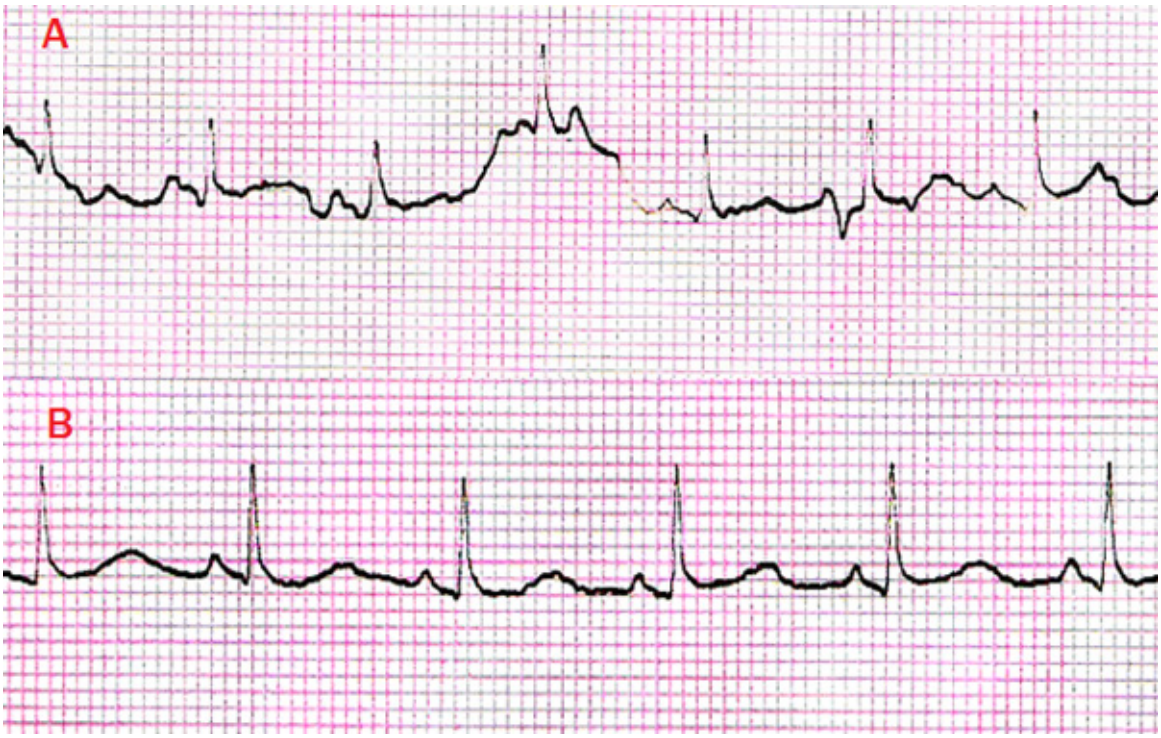

Figure 4. ECG of one cat before prescription of mexiletine (A), and ECG of the same cat after prescription of the mexiletine at a dose15 mg/kg (50 mm/s, 1 mv).

The PR interval time is one of the best coordinates for evaluating heart function, the results of which are measured in table 1 (E). According to our results, there is no significant difference in PR interval change. The PR interval in normal cats ranges from 0.05 to 0.09 seconds.

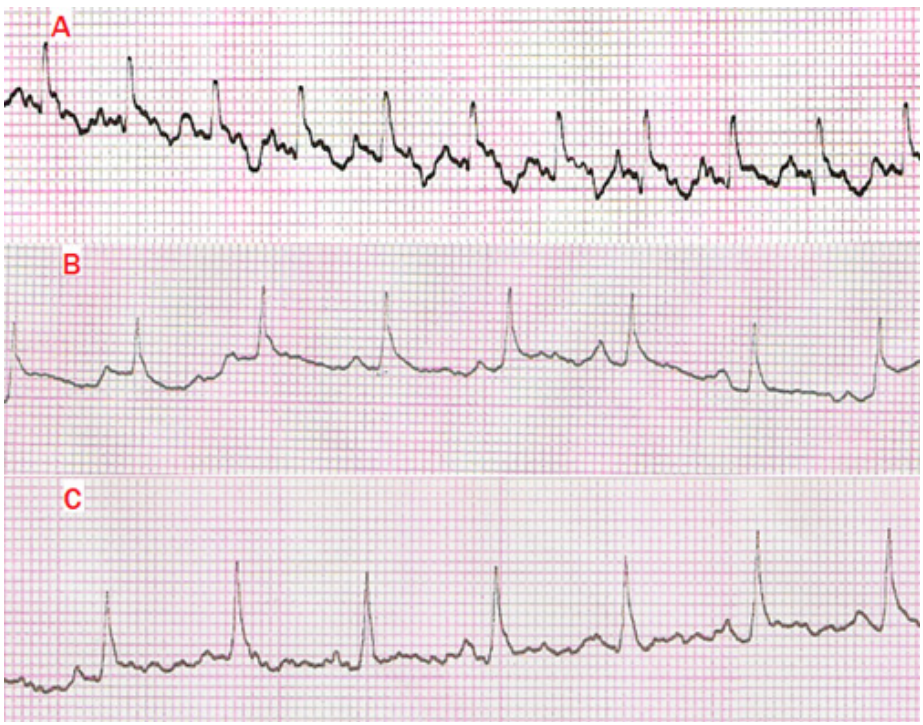

Figure 5. ECG of one cat under before prescription of the drug (A), ECG of the same cat after prescription of the drug at a dose 10 mg/kg (B),and ECG of the same cat after prescription of the mexiletine with a dose 40 mg/kg in (50 mm/s, 1 mv) (C).

In evaluating the ventricular contraction time (QT interval), after evaluating the ECGs obtained, the results are presented in Table 6. Due to the duration of this wave, which is typically from 0.11 to 0.18 seconds, no significant change has been achieved following the administration of different doses of this drug (table 1 (F)).

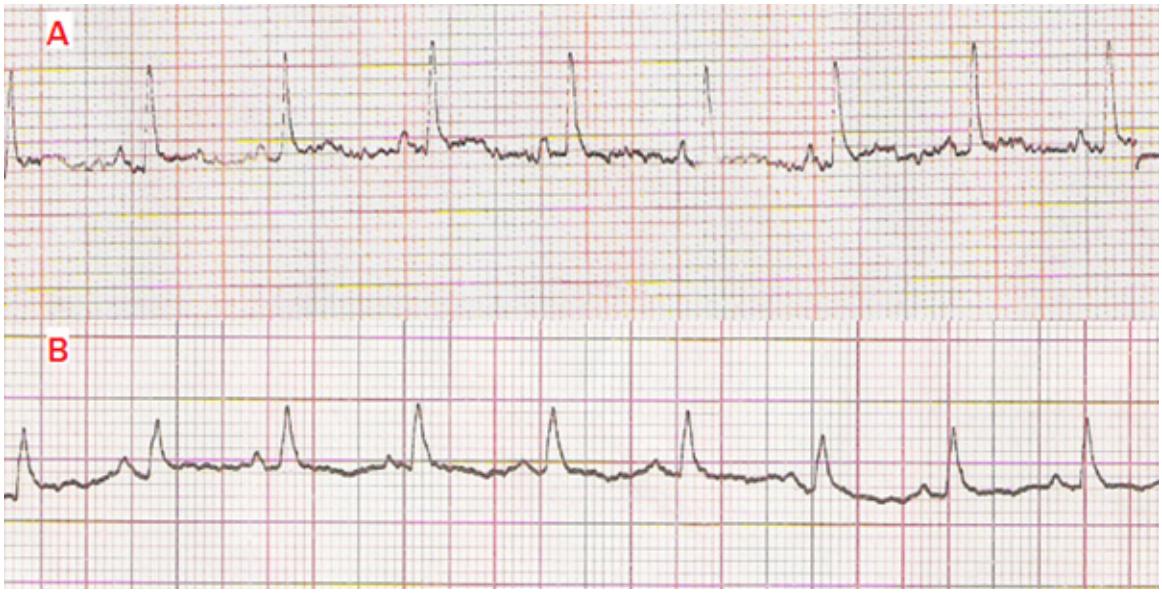

Figure 6. ECG of one cat before prescription of mexiletine (A), and ECG of the same cat after prescription of the drug with a dose 10 mg/kg (50 mm/s,1 mv) (B).

Table 1 (G) shows the heart rate in the ECG assessment of the tested cats in terms of heart rate. The results show that the heart rate varied from 111 to 333 heart beat per minutes. The heart rate appears to be highly variable both due to stress in cats and drug administration as well as the development of compensatory processes in the heart.

The results in Fig. 15 can be due to stress during ECG use or due to the heart compensatory processes due to drug administration.

In this study, a number of neurological and gastrointestinal complications have been observed due to large doses. These include temporary anorexia, tremor, obsession and incoordinance. In most cases, doses of 20 and 40 mg / kg cause symptoms of unwanted medication.

Discussion

Due to the lack of a reliable report on the effects and function of mexiletine on the electrical function of cats' heart, the effects of this drug were evaluated in this study (2).

According to the results of this study, no increase or decrease in P wave amplitude and duration was observed and all results were normal and no significant difference was observed between different doses. So it can be concluded, this drug had no major effect on atrial function and contraction. This finding is in similar with the results of other researchers (1, 2). Therefore, it can be concluded that this drug is safe for atrial function even at very high doses.

By measuring the function of incremental doses on PR interval according to the results of this study, this drug had no adverse effects on PR interval and there was no significant difference before and after drug prescription even with the use of incremental doses ($P < 0.05$).

According to the reports of different literatures on the absence of adverse drug effects on the dogs' heart function (2) and also according to the findings of the present study, it was found that on R amplitude, QRS duration and ventricular contraction time (QT interval), this drug had no adverse effects on ventricular contractions ($P<0.05$). Therefore, mexiletine had no obvious effects on ventricular contraction strength (especially left ventricle). The evaluation of QRS duration also showed that there was no significant difference between the groups in increasing doses, so that the mexiletine had no abnormal effects on ventricular contraction time ($P<0.05$). But despite a slight increase

in QT interval, this increase was in normal range. Evaluation of ventricular contraction time (QTint) also revealed no significant difference between normal ECG and after different doses (P<0.05). Therefore, increasing doses of this drug did not increase the duration of ventricular contraction.

Therefore, it can be concluded that mexiletine has no adverse effects on the severity and duration of ventricular contraction even at increasing doses. It seems that mexiletine is completely safe for heart function in normal cats, indicating its safe effects on ventricular function. This seems to be the reason for choosing of mexiletine as one of the drugs of choice for the treatment of ventricular tachyarrhythmia.

Evaluation of heart rate also showed that mexiletine was able to reduce heart rate, but this change was not associated with bradycardia and there was not a significant difference in the increase or decrease of heart rate when using incremental doses (P <0.05). In only one case at doses of 20 and 40 mg / kg was observed a decrease in heart rate, which is not very abnormal at these doses.

Therefore, according to the results of this study, it can be concluded that the drug is quite beneficial and safe for cats and no cardiac complication and electrophysiological disorder was observed even with the use of high doses or even incremental doses, so this indicates that the drug can be safe in terms of cardiac effects.

Various studies have reported unwanted gastrointestinal and neurological complications while using this drug (6, 7). These studies show that the side effects are dose-related and reversible. Common complications observed in various reports include nausea, anorexia, head tilt and limb tremor, imbalance and incoordinance (2).

In this study, some of the complications mentioned in the tested cats were observed. However, these complications are individual and are usually observed at very high doses, such as 20 and 40 mg / kg. The most common complications observed in this study include temporary anorexia, tremor, obsession and imbalance. However, all of these effects were temporary and no side effects were observed when the next dose was administered or in drug wash out time. It is also suggested that the drug be used with foods to minimize the risk of drug side effects, as suggested by various studies to minimize the side effects.

However, in order to minimize drug complications in cats, a review of safe doses with a greater number of cats is needed. It seems that investigating different drug doses, as well as measuring the left ventricular ejection fraction in cats, may be helpful in adjusting the dose required in cats.

According to the results of this study, it is recommended to re-evaluate the appropriate pharmacological effects of this drug for treatment of cats with supra or ventricular tachyarrhythmia and the results to be reviewed. In addition, it is recommended to determine the necessary and safe doses for cats and it is necessary to determine the proper and therapeutic doses by HPLC.

Ethical Clearance: The ethical permission was taken from the ethic committee of faculty of veterinary medicine, Islamic Azad University Tabriz Branch.

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Conflict of Interest: There is no conflict of interests in this project.

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