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# Study of co-administration of Fexofenadine and fluconazole induced electrocardiogram changes in Dog

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## ABSTRACT

*Side effect of antihistamines in humans and animals are numerous and the most effects of these drugs that have been reported are cardiovascular effects such as ventricular fibrillation and death due to prolonged QT and abnormal ventricular arrythmies with some antihistamines. According to clinical applications fexofenadine and other antihistamines in control of atopic and allergic dermatitis in dogs and the importance of replacing antihistamine instead of corticosteroids.In present study first of all dogs electrocardiogram at day zero were obtained and then these dogs divided to two groups, in first group each dogs eat 3mg/kg BW (orally) fexofenadine for 7 consecutive days. In second group 18mg/kg Fexofenadine and fluconazole (orally) for 7 consecutive days were administrated. Immediately after the last dose, at times 0,2,6 and 8 hours after administration ECG were obtained of treated dogs. In the present study we observed that fexofenadine with all strength can decrease heart rate during times of 2, 6 and 8 hours after dosing which is followed by increase of factors like distance RR, PR and QT interval, finally results of this study induced bradycardia and decreased heart rate after orally administration of fexofenadine.Taking antihistamines, especially blockers $H_1$ antihistamines should be done with caution in patients with heart decrease in dogs and dogs with heart worm disease and avoid using long time of these compounds and before using these drugs in dogs with atopic dermatitis, electrocardiogram is required for a healthy test, then fexofenadine is administrated.*

**Key words:** fexofenadine,fluconazole, dog, electrocardiogram.

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## INTRODUCTION

Antihistamines are $H_1$ blocker which is used in human and veterinary medicine and in humans to treatment of allergic signs such as pruritus and anaphylactic reactions. Also they used as sedative and antiemetic drugs (6). Antihistamines divided into first and second generation; first-generation antihistamines are small lipophilic molecules and due to the ease crossing from blood

brain barrier have many cholinergic side effects (3). But second-generation antihistamines due to uncrossing from blood brain barrier have lower side effects at therapeutic doses. Side effects of antihistamines in humans and animals is widespread and of most important effects of these drugs can be refer to cardiovascular effects such as ventricular fibrillation and death due to long QT and abnormal ventricular tachycardia arrhythmias with some antihistamines have been reported.However, such changes in terfenadine and astemizole are more severe (2).Activity and pharmacokinetics of antihistamines is altered by hepatic P450 enzymes inhibitors, including subfamily CYP3A that caused in increasing of drug accumulation in the body and induction of "Torsa de Pointes" phenomena and various life-threatening arrhythmias. Of these drugs which are induce mentioned effects can be refer to systemic anti-fungal compounds.Ketoconazole can inhibit CYP3A but inhibitory effects of fluconazole have been determined in vitro. According to clinical applications of fexofenadine and other antihistamines with systemic antifungal such as fluconazole in controlling of atopic dermatitis and allergic diseases and other disorders related to histamine release in the dogs and the importance of replacement the antihistamines instead of corticosteroids and methylprednisolone in treatment of above diseases, we aimed to study of cardiac effects due to the concurrent administration of fluconazole and fexofenadine on heart performance of dogs (13). In one study by Plevink et al., (2006) revealed that fexofenadine is safe and effective in treatment of atopic dermatitis in dogs than methylprednisolone (5).In a study on 44 dogs was determined that Fexofenadine in five treated dogs cause mild to slight depression and was determined that these effects was more evident in west highland white terier and mainly caused severe tachycardia, tachypnea, dyspnea and Ataxia (1). Yoshihide et al., (2003) were studied some effects of antihistamines in dogs and cats and reported that terfenadine in dogs has proarrhythmic effects (8). In Peter et al., (1993) study was determined that the concomitant use of ketoconazole with changes in terfenadine pharmacokinetics yields to changes in electrocardiogram and Q-T intervals (4). In Pohja et al., (1993) study demonstrated that itraconazole by inhibition of terfenadine metabolism can increase occurrence risk of "Torsa des pointes" and ventricular tachycardia (7).

## MATERIALS AND METHODS

In this study (experimental-invasive) 12 dogs were selected and used by chance. Before beginning research, clinical examination of animals taken from health aspects and cardiac auscultation were done and if there were any congenital problems such as murmurs and possible contamination to dirofilariaimmitis and after observation of abnormal ECG, suspected dogs was removed from study. In clinical examinations related to heart, kidneys and liver no observed any disorder. After primary examinations, the dogs were weighted and treated with mebendazole 100mg at the dose of 20mg/kg for 1 week to minimizing the parasitic contaminations. It must be noted that the average weight of dogs was considered 20-25 kg and their age range between 2-3 years to prevention of age bias on results.Dogs were divided into the two groups of six dogs. First, of all dogs on day 1 ECG were taken and then in group 1 each dogs received oral fexofenadine 3mg/kgBW for 7 days consecutively and group 2 received oral fexofenadine 3mg/kgBW and oral fluconazole 12mg/kgBWfor 7 days consecutively. Immediately after the last dose at the time of, 2, 4 and 8 hours after dosing of treated dogs, ECG were obtained. For obtaining an electrocardiogram before starting study, dogs in trine groups has been transported to other room to minimizing the tension, esters and other factors. To obtaining the ECG, dogs without anesthesia and stress laid in right side and ECG were achieved. Data were presented as

Mean±SEM and for analyzing the data were used of ANOVA test and to comparison of data were used of TUKEY test. P<0.05 were considered as significant difference.

## RESULTS AND DISCUSSION

Primary obtained data are listed in table 1.

***Comment of result related to Q-T interval at the times of 0,2,6 and 8 hours after oral administration of fexofenadine 3mg/kg***

Although Q-T interval in all times during the study after administration of fexofenadine 3mg/kg was in normal boundary but Q-T interval between times 0 and 8 was significant (P<0.05) and this distance was greater than similar distance at time 0.

***Comment of result related to Q-T interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine-fluconazole***

Q-T interval in times of 2 and 6 hours after co-administration of fexofenadine- fluconazole was increased and was significant (P<0.05), but in 8 hours after administration any significant different was not observed. Also changes belong to this distance between times of 2 with 6hours, 2 with 8hours and 6 with 8hours was not significant.

***Comparison of result related to Q-T interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine- fluconazole withoral administration of fexofenadine***

Any significant different between to Q-T interval at the times of 0, 2, 6 and 8 hours after oral co-administration of fexofenadine- fluconazole with oral administration of fexofenadine was not observed.

**Table 1: primary data obtained from ECG of dogs**

| Dose/time | HR | $PR_{int.}$ | $QRS_{D.}$ | $P_D$ | $P_A$ | $R_A$ | $RR_{int.}$ | $QT_{int.}$ |
|---|---|---|---|---|---|---|---|---|
| **fexo3-0** | 100 | 0.12 | 0.05 | 0.04 | 0.2 | 1 | 0.52 | 0.2 |
| **fexo3-0** | 120 | 0.12 | 0.04 | 0.04 | 0.2 | 1 | 0.58 | 0.2 |
| **fexo3-0** | 110 | 0.1 | 0.04 | 0.04 | 0.2 | 1 | 0.52 | 0.18 |
| **fexo3-0** | 110 | 0.1 | 0.05 | 0.04 | 0.2 | 1.2 | 0.48 | 0.2 |
| **fexo3-0** | 100 | 0.12 | 0.05 | 0.04 | 0.2 | 1.2 | 0.48 | 0.2 |
| **fexo3-0** | 110 | 0.1 | 0.04 | 0.04 | 0.2 | 1 | 0.52 | 0.18 |
| **fexo3-2** | 80 | 0.14 | 0.05 | 0.04 | 0.2 | 1.8 | 0.84 | 0.22 |
| **fexo3-2** | 80 | 0.14 | 0.04 | 0.04 | 0.2 | 1.5 | 0.86 | 0.26 |
| **fexo3-2** | 70 | 0.14 | 0.05 | 0.04 | 0.2 | 1.5 | 0.65 | 0.2 |
| **fexo3-2** | 70 | 0.14 | 0.04 | 0.04 | 0.2 | 1.9 | 0.8 | 0.22 |
| **fexo3-2** | 80 | 0.14 | 0.05 | 0.04 | 0.2 | 1.5 | 0.65 | 0.2 |
| **fexo3-2** | 70 | 0.14 | 0.05 | 0.04 | 0.2 | 1.5 | 0.65 | 0.2 |
| **fexo3-6** | 60 | 0.18 | 0.05 | 0.04 | 0.2 | 1.5 | 0.96 | 0.22 |
| **fexo3-6** | 80 | 0.16 | 0.04 | 0.04 | 0.2 | 1.5 | 0.76 | 0.22 |
| **fexo3-6** | 70 | 0.14 | 0.05 | 0.04 | 0.2 | 1.5 | 0.64 | 0.2 |
| **fexo3-6** | 60 | 0.16 | 0.04 | 0.04 | 0.2 | 1.5 | 0.95 | 0.22 |
| **fexo3-6** | 60 | 0.18 | 0.05 | 0.04 | 0.2 | 1.5 | 0.64 | 0.22 |
| **fexo3-6** | 70 | 0.14 | 0.05 | 0.04 | 0.2 | 1.5 | 0.64 | 0.2 |
| **fexo3-8** | 60 | 0.16 | 0.05 | 0.04 | 0.1 | 1.2 | 0.82 | 0.22 |
| **fexo3-8** | 80 | 0.16 | 0.04 | 0.04 | 0.2 | 1.2 | 0.64 | 0.22 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **fexo3-8** | 80 | 0.15 | 0.05 | 0.04 | 0.2 | 1.2 | 0.6 | 0.22 |
| **fexo3-8** | 60 | 0.16 | 0.04 | 0.04 | 0.2 | 1.5 | 0.8 | 0.22 |
| **fexo3-8** | 80 | 0.16 | 0.05 | 0.04 | 0.2 | 1.2 | 0.65 | 0.22 |
| **fexo3-8** | 80 | 0.15 | 0.05 | 0.04 | 0.2 | 1.2 | 0.6 | 0.22 |
| **ff-0** | 100 | 0.1 | 0.04 | 0.02 | 0.2 | 1 | 0.56 | 0.2 |
| **ff-0** | 100 | 0.1 | 0.04 | 0.04 | 0.2 | 1 | 0.57 | 0.2 |
| **ff-0** | 120 | 0.1 | 0.04 | 0.02 | 0.1 | 1.1 | 0.55 | 0.2 |
| **ff-0** | 100 | 0.1 | 0.04 | 0.04 | 0.2 | 1.2 | 0.6 | 0.2 |
| **ff-0** | 100 | 0.1 | 0.04 | 0.02 | 0.2 | 1.1 | 0.55 | 0.2 |
| **ff-0** | 120 | 0.1 | 0.04 | 0.02 | 0.1 | 1.1 | 0.55 | 0.2 |
| **ff-2** | 80 | 0.14 | 0.04 | 0.02 | 0.2 | 1.5 | 1.21 | 0.24 |
| **ff-2** | 60 | 0.14 | 0.05 | 0.02 | 0.1 | 0.8 | 0.83 | 0.26 |
| **ff-2** | 60 | 0.16 | 0.05 | 0.02 | 0.2 | 0.8 | 1.22 | 0.26 |
| **ff-2** | 60 | 0.14 | 0.04 | 0.04 | 0.2 | 1.3 | 1.2 | 0.26 |
| **ff-2** | 60 | 0.16 | 0.05 | 0.02 | 0.2 | 0.9 | 1.66 | 0.26 |
| **ff-2** | 60 | 0.16 | 0.05 | 0.02 | 0.2 | 0.8 | 1.22 | 0.26 |
| **ff-6** | 60 | 0.16 | 0.04 | 0.04 | 0.2 | 1.2 | 1.18 | 0.26 |
| **ff-6** | 80 | 0.14 | 0.05 | 0.04 | 0.1 | 1 | 0.83 | 0.24 |
| **ff-6** | 60 | 0.18 | 0.05 | 0.04 | 0.1 | 0.5 | 1.15 | 0.28 |
| **ff-6** | 60 | 0.16 | 0.05 | 0.04 | 0.2 | 1.1 | 1.35 | 0.26 |
| **ff-6** | 80 | 0.18 | 0.05 | 0.04 | 0.2 | 0.7 | 1.22 | 0.28 |
| **ff-6** | 60 | 0.18 | 0.05 | 0.04 | 0.1 | 0.5 | 1.15 | 0.28 |
| **ff-8** | 80 | 0.14 | 0.05 | 0.02 | 0.1 | 1.3 | 1.07 | 0.24 |
| **ff-8** | 80 | 0.12 | 0.05 | 0.02 | 0.1 | 0.8 | 0.78 | 0.24 |
| **ff-8** | 60 | 0.16 | 0.05 | 0.02 | 0.2 | 0.9 | 1.06 | 0.26 |
| **ff-8** | 80 | 0.14 | 0.05 | 0.04 | 0.2 | 1.1 | 0.98 | 0.23 |
| **ff-8** | 80 | 0.16 | 0.05 | 0.02 | 0.2 | 0.9 | 1.06 | 0.26 |
| **ff-8** | 60 | 0.16 | 0.05 | 0.02 | 0.2 | 0.9 | 1.06 | 0.26 |

*HR= Heart Rate*
*PR int. = PR Interval*
*$QRS_D$ = QRS Duration*
*$P_D$= P Duration*
*$P_A$= P Amplitude*
*$R_A$ = R Amplitude*
*RR int. = RR Interval*
*QT int. = QT Interval*

***Comment of result related to R-R interval at the times of 0,2,6 and 8 hours after oral administration of fexofenadine 3mg/kg***

After administration of fexofenadine 3mg/kg, R-R interval began to significantly increase 2 and 6 hours after administration ($P<0.05$). But, no observed significant difference in R-R interval 8 hours after administration. Also differences related to R-R interval at times 2-6, 2-8 and 6-8 hours after administration wasn't significant.

***Comment of result related to R-R interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine-fluconazole***

R-R interval in times of 2 and 6 hours after co-administration of fexofenadine- fluconazole was increased and was significant ($P<0.05$), but in 8 hours after administration any significant different was not observed. Also changes belong to this distance between times of 2 with 6hours, 2 with 8hours and 6 with 8hours was not significant.

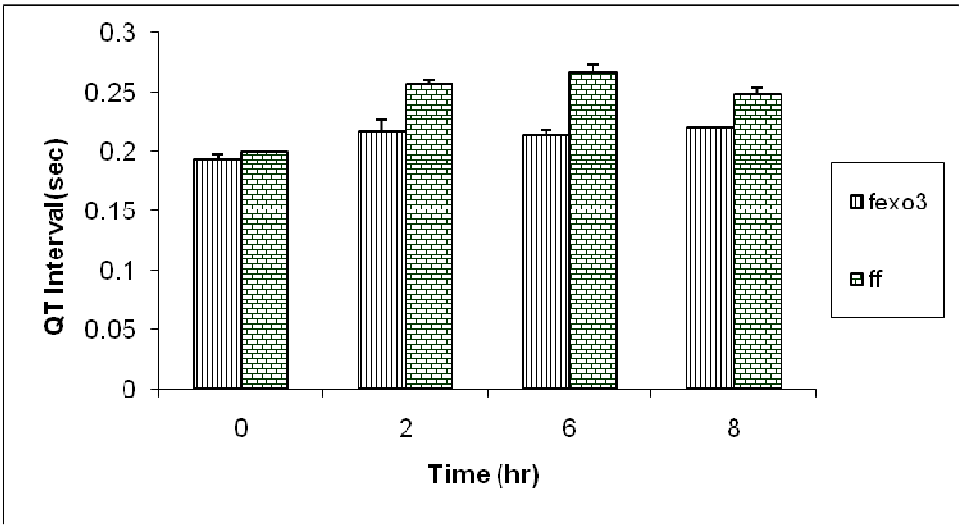



**Diagram 1: comparative diagram of Q-T interval subsequent fexofenadine oral administration andoral co-administration of fexofenadine- fluconazole at times 0, 2, 6 and 8.**

***Comparison of result related to R-R interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine- fluconazole withoral administration of fexofenadine***

Any significant different between to R-R interval at the times of 0, 2, 6 and 8 hours after oral co-administration of fexofenadine- fluconazole with oral administration of fexofenadine was not observed.

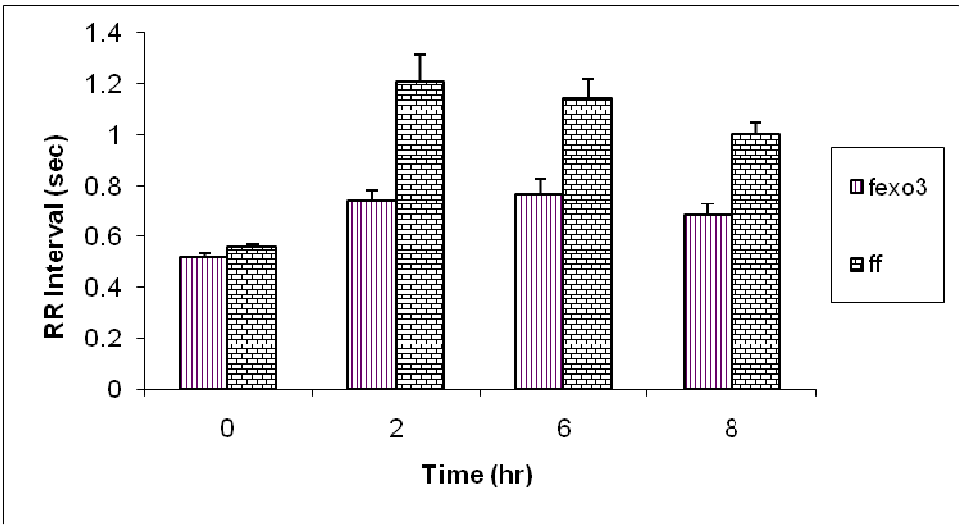



**Diagram 2: comparative diagram of R-R interval subsequent fexofenadine oral administration andoral co-administration of fexofenadine- fluconazole at times 0, 2, 6 and 8.**

***Comment of result related to HR at the times of 0,2,6 and 8 hours after oral administration of fexofenadine 3mg/kg***

Changes related to HR between time 0 and 2, 0 and 6, 0 and 8 hours after oral administration of fexofenadine was significant (P<0.001). Oral administration of fexofenadine caused severe bradycardia in dogs. Thus can be claim that bradycardia is one result of the fexofenadine 3mg/kg oral administration. In this period no observed significant difference between time 0-6, 2-8 and 6-8 after administration of fexofenadine 3mg/kg.

***Comment of result related to HR at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine-fluconazole***

HR interval in times of 2 and 6 hours after co-administration of fexofenadine- fluconazole was increased and was significant (P<0.05), but in 8 hours after administration any significant different was not observed. Also changes belong to this distance between times of 2 with 6hours, 2 with 8hours and 6 with 8hours was not significant.

***Comparison of result related to HR at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine- fluconazole withoral administration of fexofenadine***

Any significant different between to HR at the times of 0, 2, 6 and 8 hours after oral co-administration of fexofenadine- fluconazole with oral administration of fexofenadine was not observed.

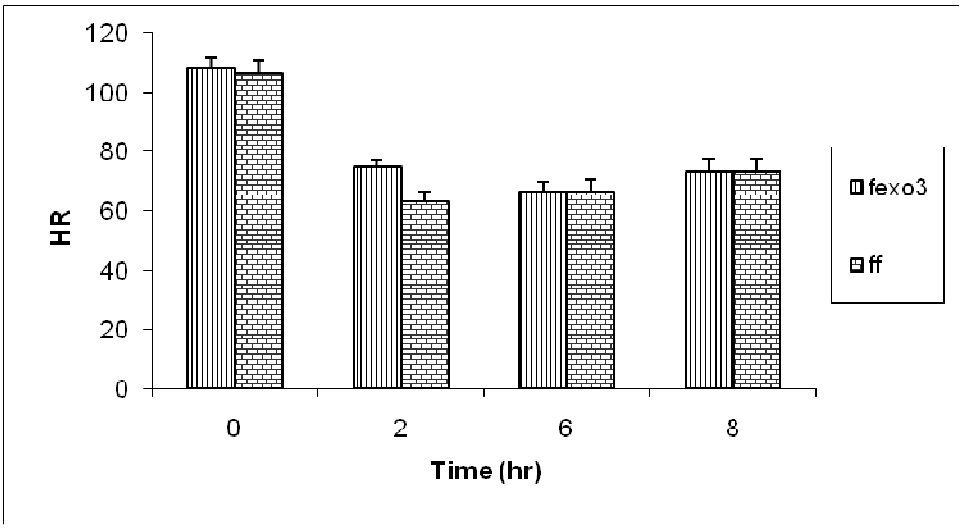



**Diagram 3: comparative diagram of HR subsequent fexofenadine oral administration andoral co-administration of fexofenadine- fluconazole at times 0, 2, 6 and 8.**

***Comment of result related to P-R interval at the times of 0,2,6 and 8 hours after oral administration of fexofenadine 3mg/kg***

In all times (2,6 and 8 hour) after administration of fexofenadine 3mg/kg P-R interval was increased from normal range and was observed a heart block type I. Statistically, P-R interval between times 0-8 and 0-6 hours after oral administration was significantly increased (P<0.05). It seems that this behavior is due to bradycardic effect of fexofenadine on heart performance.

***Comment of result related to P-R interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine-fluconazole***

In all times (2,6 and 8 hour) after co-administration of fexofenadine- fluconazole P-R interval was increased from normal range and was observed a heart block.Statistically,P-R interval in times 2 and 6 hours after oral administration was significantly increased ($P<0.05$).In this period no observed significant difference between time 0-6, 2-8 and 6-8 afteroral co-administration of fexofenadine- fluconazole.

***Comparison of result related to P-R interval at the times of 0,2,6 and 8 hours after oral co-administration of fexofenadine- fluconazole withoral administration of fexofenadine***

Any significant different between to P-R interval at the times of 0, 2, 6 and 8 hours after oral co-administration of fexofenadine- fluconazole with oral administration of fexofenadine was not observed.

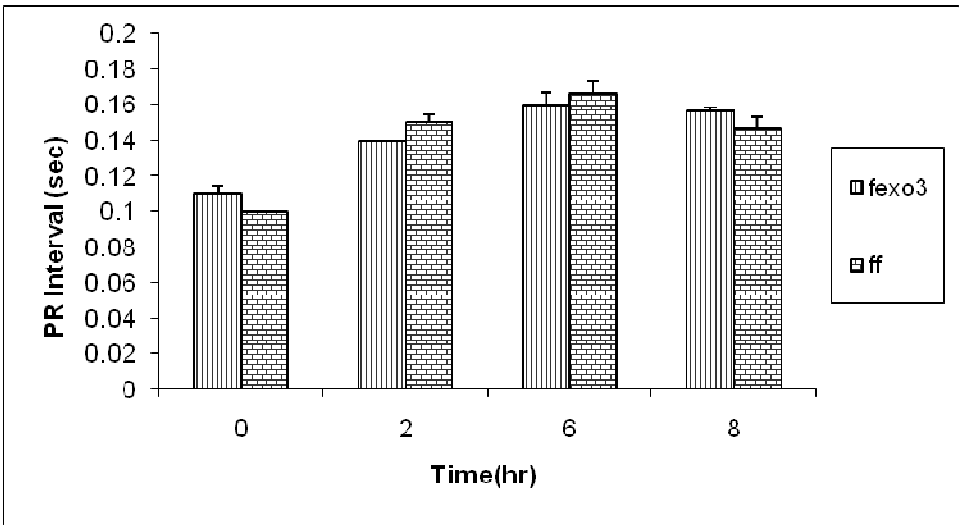
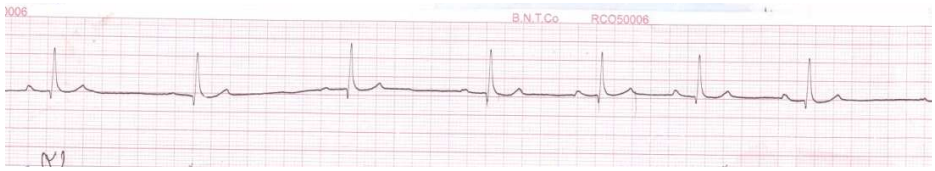
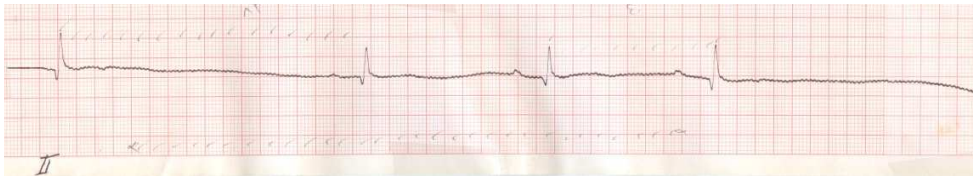



**Diagram 4: comparative diagram of P-R interval subsequent fexofenadine oral administration andoral co-administration of fexofenadine- fluconazole at times 0, 2, 6 and 8.**

Also afterco-administration of fexofenadine- fluconazole in all times one intensive arrhythmia (Sinus Arrest) were observed which was very intensive in comparison with administration of fexofenadine 3 mg/kg.



**Example of normal dogs ECG at the time of 0.**



**Example of dog's ECG subsequent oral co-administration of fexofenadine- fluconazole.**

According to routine antihistamines application to treatment of dog's atopic dermatitis and importance and necessity of replacing these compounds instead of corticosteroids which have more efficacy than antihistamines in treatment of allergies, obviously, study on side effects of anti-histamines compounds which are mainly on heart function (2) has great importance. In current study the effect of fexofenadine and oral co-administration of fexofenadine- fluconazole on heart performance was studied and demonstrated that this anti-histamines potentially yields to decrease in HR at different times after administration that followed by increase in R-R, P-R and Q-T intervals. In general, the objective of this study was induction of bradycardia and reduction of HR subsequent oral administration of fexofenadineand oral co-administration of fexofenadine-fluconazole. This research results is consistent with other similar. In one study by Takahara et al., 2006 on heart performance of treated dogs with terfenadine demonstrated that this drug can cause bradycardia and atrioventricular blocks and increase in P-R interval that is same with present study (14). In one other study by Falgun et al., 2010 on Q-T interval subsequent use of fexofenadine revealed that this compound can cause increase in Q-T interval and prone patient heart to torsade de pointes type of arrhythmia. In one other study was observed that terfenadine can yields to severe falling of HR or induction of bradycardia. This finding is true about both low and high dose of terfenadine. Fexofenadine is active metabolite of terfenadine which acts as histamine receptors antagonist and because of this reason has same effects as terfenadine (11,12). Terfenadine and its related antihistamines have multiple cardiovascular effects and exert their cardiac effects through various mechanisms. These anti-histamines through inhibition of several calcium channels exert their concurrent effects with calcium and yields to induction of negative inotropic and chronotropic on heart function. This is based on Liu et al research result (9). One other action mechanism of these anti-histamines is block of potassium channels exist in atrial and ventricular myocytes (10,15). Finally, can be conclude that administration of $H_1$-blockers anti-histamines in patients with cardiovascular disorders must be limited and prevented of long-term usage of these anti-histamines in this patients.

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