Middle-East Journal of Scientific Research 9 (4): 472-477, 2011
ISSN 1990-9233

Effect of Fexofenadine on Dog's Heart Performance

[1]Neshat Gharamaleki Mehrdad, [2]Nabizadeh Behrouz and [3]Safarmashaei Saeid

[1]Department of Clinical Science, Tabriz branch, Islamic Azad University, Tabriz, Iran
[2]Postgraduate Student of Veterinary Medicine, Tabriz branch, Islamic Azad University, Tabriz, Iran
[3]Young Researchers Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran

Abstract: Antihistamines are H_1 blocker which is used in human and veterinary medicine. In humans for treatment of allergic signs such as pruritus and anaphylactic reactions. The aim of this study was to evaluate fexofenadine effect on dog's heart performance. In this study 12 dogs were selected and Divided randomly into two groups, control and fexofenadine groups. Fexofenadine was given at two dose levels (3 and 18 mg/kg b.wt.) fexofenadine at the dose of the 3 and 18 mg/kgBW were administrated. In this study, the results revealed that fexofenadine has dose-independent effect on heart performance. It can be concluded that that administration of H_1-blockers as anti-histamincs in patients with cardiovascular disorders must be limited and prevented of long-term usage in the patients in this patients.

Key words: Fexofenadine · Dog · Heart Performance

INTRODUCTION

Antihistamines are H_1 blocker which is used in human and veterinary medicine and in humans for treatment of allergic signs such as pruritus and anaphylactic reactions. Also they used as sedative and antiemetic drugs [1]. 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 [2]. 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 which can be refer to cardiovascular effects such as ventricular fibrillation and death due to long Q-T interval and abnormal ventricular tachycardia arrhythmias with some antihistamines have been reported. However, such changes in terfenadine and astemizole are more severe [3]. 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 the cardiac effects due to the concurrent administration of fluconazole and fexofenadine on heart performance of dogs [4]. In one study by Plevink *et al.* revealed that fexofenadine is safe and effective in treatment of atopic dermatitis in dogs than methylprednisolone [5]. In a study on 44 dogs, it 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 [6]. Yoshihide *et al.* were studied some effects of antihistamines in dogs and cats and reported that terfenadine in dogs has proarrhythmic effects [7]. In Peter *et al.* study, they reported that the concomitant use of ketoconazole with changes in terfenadine pharmacokinetics yields to changes in electrocardiogram and Q-T intervals [8]. In Pohja *et al.* study demonstrated that itraconazole by inhibition of terfenadine metabolism can increase occurrence risk of "Torsa des pointes" and ventricular tachycardia [9].

Corresponding Author: NeshatGharamaleki Mehrdad, Department of clinical science, Tabriz branch, Islamic Azad University, Tabriz, Iran.

MATERIAL AND METHODS

In this study (experimental-invasive) 12 dogs were selected and used randomly. 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 dirofilaria immitis and after observation of abnormal ECG, suspected dogs was excluded from study. In clinical examinations related to heart, kidneys and liver no observed any disorder. After primary examinations, the dogs were weighed and treated with mebendazole 100mg at the dose of 20mg/kg b.wt. 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 for prevention of age bias on results. Dogs were divided into the two groups of six dogs. First, all dogs on day 1 ECG were taken and then in group 1 each dogs received oral fexofenadine 3mg/kg, b. wt. for 7 days consecutively and group 2 received fexofenadine 18mg/kg b. wt. for 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.

Statistical Analyses: Data were presented as Mean±SE 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

Primary obtained data are listed in Table 1.

Effect of Fexofenadine 3mg/kg b.wt. On HR.: 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 oral administration of the fexofenadine 3mg/kg. In this period no significant difference was observed between time 0-6, 2-8 and 6-8 after administration of fexofenadine 3mg/kg.

Effect of Fexofenadine 18mg/kg b.wt. on HR.: HR was decreased significantly ($P<0.05$) After 2 and 8 hours oral administration of fexofenadine 18mg/kg b. wt.. Merged with previous statement HR reduction 6 hours after administration wasn't significant and no observed significant different between times 2-6, 6-8 and 2-8hrs after administration.

Comparison of Result Related to HR at Times 0,2,6 and 8 Hours after Oral Administration of Fexofenadine 3 and 18mg/kg: No significant difference was observed on HR between Two doses of fexofenadine(3 & 18 mg/kg b.wt.) along different intervals from treatment(0,2,and 8hrs) in fexofenadine 3mg/kg and 18mg/kg groups. This finding suggests fexofenadine dose-independent effect on HR (Diagram 1).

Effect of Fexofenadine 3mg/kg b.wt. on R-R Interval: 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.

Effect of Fexofenadine 18mg/kg b.wt. on R-R Interval: After administration of 18mg/kg b.wt. fexofenadine, R-R interval began to significantly increase 2 and 8 hours after administration ($P<0.05$). But, no observed significant difference in R-R interval 6 hours after administration. Also differences related to R-R interval after administration of fexofenadine 18mg/kg wasn't significant at times 2-6, 2-8 and 6-8 hours.

Comparison of Result Related to R-R Interval at Times 0,2,6 and 8 Hours after Oral Administration of Fexofenadine 3 and 18mg/kg: No observed significant difference about R-R interval between different times in fexofenadine 3mg/kg and 18mg/kg groups. This finding suggests fexofenadine dose-independent effect on R-R interval (Diagram 2).

Effect of Fexofenadine 3mg/kg b.wt. on Q-T Interval: 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.

Effect of Fexofenadine 18mg/kg b.wt. on Q-T Interval: Although Q-T interval at different times after the oral administration of Fexofenadine 18mg/kg is in normal range

Table 1: Primary data obtained from ECG of dogs which are treated with fexofenadine (3 and 18mg/kg, b.wt.).

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
fexo18-0	100	0.1	0.04	0.04	0.2	1	0.54	0.2
fexo18-0	95	0.12	0.04	0.04	0.2	1.1	0.6	0.22
fexo18-0	90	0.12	0.04	0.04	0.1	1.1	0.5	0.2
fexo18-0	100	0.12	0.04	0.04	0.1	1.2	0.54	0.2
fexo18-0	90	0.12	0.05	0.04	0.2	1.2	0.5	0.18
fexo18-0	90	0.12	0.04	0.04	0.1	1.1	0.5	0.2
fexo18-2	60	0.22	0.05	0.04	0.2	1.5	1.51	0.2
fexo18-2	60	0.16	0.05	0.04	0.2	1.3	0.77	0.22
fexo18-2	60	0.18	0.05	0.04	0.2	1.2	1	0.26
fexo18-2	60	0.16	0.04	0.04	0.2	1	1.17	0.26
fexo18-2	60	0.16	0.05	0.04	0.1	1.1	0.85	0.22
fexo18-2	60	0.18	0.05	0.04	0.2	1.2	1	0.26
fexo18-6	60	0.16	0.04	0.04	0.2	1.5	1.2	0.22
fexo18-6	80	0.14	0.04	0.04	0.2	1.2	0.6	0.22
fexo18-6	60	0.16	0.05	0.04	0.2	1.1	1.05	0.24
fexo18-6	80	0.14	0.05	0.04	0.2	1.2	0.8	0.22
fexo18-6	80	0.14	0.05	0.04	0.1	1.1	0.76	0.2
fexo18-6	60	0.16	0.05	0.04	0.2	1.1	1.05	0.24
fexo18-8	60	0.2	0.05	0.02	0.1	1.2	1.16	0.2
fexo18-8	60	0.14	0.05	0.04	0.2	1.3	0.85	0.22
fexo18-8	60	0.2	0.05	0.04	0.2	1.2	1.6	0.26
fexo18-8	65	0.15	0.05	0.04	0.2	1	0.95	0.22
fexo18-8	60	0.18	0.05	0.04	0.2	1	0.96	0.22
fexo18-8	60	0.2	0.05	0.04	0.2	1.2	1.6	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

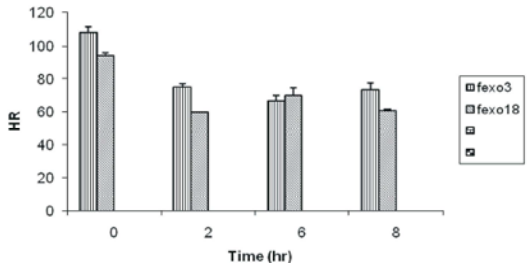


Diagram 1: Comparative diagram of HR subsequent fexofenadine 3 and 18mg/kg oral administration at times 0,2,6 and 8hrs.

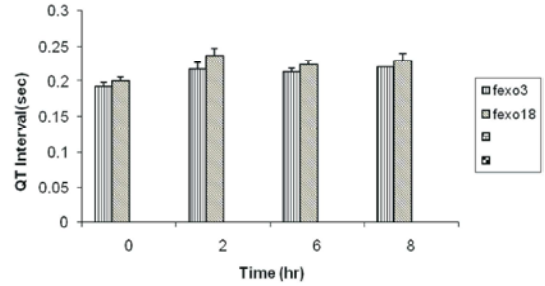


Diagram 3: Comparative diagram of Q-T interval subsequent fexofenadine 3 and 18mg/kg oral administration at times 0,2,6 and 8hrs.

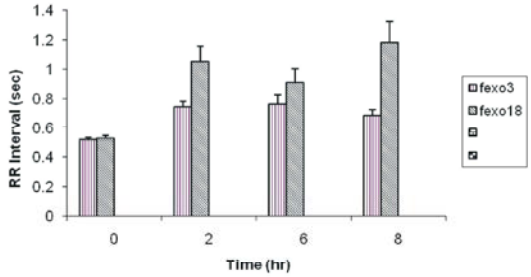


Diagram 2: Comparative diagram of R-R interval subsequent fexofenadine 3 and 18mg/kg oral administration at times 0,2,6 and 8.

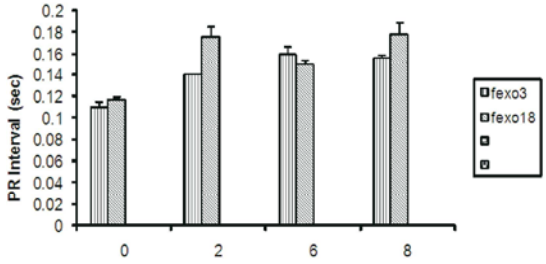
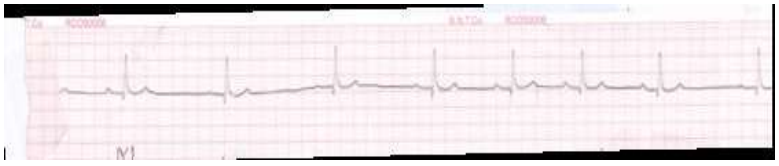
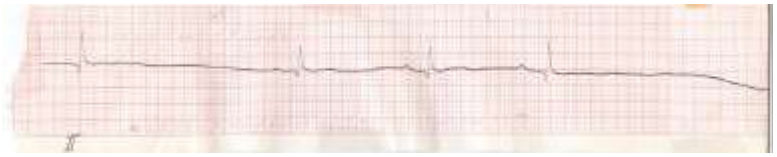


Diagram 4: Comparative diagram of P-R interval subsequent fexofenadine 3 and 18mg/kg oral administration at times 0,2,6 and 8hrs.



Example of normal dogs ECG at the time of 0.



Example of dog's ECG subsequent administration of fexofenadine. As seen, R-R and P-R intervals was increased.

but the Q-T interval between times 0-2 hours after oral administration was significant ($P<0.05$) and this distance was greater than similar distance at time 0.

Comparison of Result Related to Q-T Interval at Times 0,2,6 and 8 Hours after Oral Administration of Fexofenadine 3 and 18mg/kg: No significant difference was observed on Q-T interval between different times in fexofenadine 3mg/kg and 18mg/kg groups. This finding suggests fexofenadine dose-independent effect on Q-T interval (Diagram 3).

Effect of Fexofenadine 3mg/kg b.wt. on P-R Interval: 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.

Effect of Fexofenadine 18mg/kg b.wt. on Q-T Interval: 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, 2 and 0-6 hours after oral administration (18mg/kg) was significantly increased ($P<0.05$). No observed any significant difference between times 2,6 and 8. Thus, can be concluded that this behavior also is due to decrease in HR.

Comparison of Result Related to P-R Interval at Times 0,2,6 and 8 Hours after Oral Administration of Fexofenadine 3 and 18mg/kg: No observed significant difference about P-R interval between different times in fexofenadine 3mg/kg and 18mg/kg groups. This finding suggests fexofenadine dose-independent effect on P-R interval (Diagram 4).

Also, subsequent administration of fexofenadine 18mg/kg especially at the times 6 and 8 hours was observed situation which called sinus arrest.

DISCUSSION AND CONCLUSION

According to routine antihistamines application for 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 has great importance [3]. In current study the effect of fexofenadine on heart performance was studied and demonstrated that this anti-histamines potentially leads 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 fexofenadine. This research results is consistent with other similar studies. In one study by Takahara *et al.* 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 in agreement with the present finding [10]. In another study by Falgun *et al*. [11] 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 addition, It was found that terfenadine can leads to severe falling in HR or induction of bradycardia. This finding is true about both low and high doses of terfenadine. Fexofenadine is active metabolite of terfenadine which acts as histamine receptors antagonist and because of this reason has same effects as terfenadine [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 [13]. One other mechanism of action of these anti-histamines is block of potassium channels exist in atrial and ventricular myocytes [14,15]. 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 the patients.

REFERENCES

1. Lorenz, P.T., Dogs electrocardiography, translated by Rezakhani, A. Shiraz, Shiraz University publication, 2nd Edition, 21-25, 39-64. (in press)
2. AHFS Drug Information, 2000. American Society of Health-System Pharmacists, Bethesda, Md. 2000. pp: 2-45.
3. Babe, Jr. K.S. and W.E. Serafin, 1996. Histamine, bradykinin and their antagonists. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed. (J.G. Hardman; L.E. Limbird, eds.). McGraw- Hill, New York, NY, pp: 586-5.
4. Gonzalez, M.A. and K.S. Estes, 1998. Pharmacokinetic overview of oral second-generation H1 antihistamines. Int. J. Clin. Pharmacol. Ther., 36: 292-300.
5. Honig, P.K., *et al*. 1993. Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA, 269: 1513-1518.
6. Honig P.K., D.C. Wortham, *et al.* 1993. Intraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. J. Clin. Pharmacol., 33: 1201-1206.
7. Kishimoto, W., T. Hiroi, K. Sakai, Y. Funae and T. Igarashi, 1997. Metabolism of epinastine, a histamine H1 receptor antagonist, in human liver microsomes in comparison with that of terfenadine. Res. Commun. Mol. Pathol. Pharmacol., 98: 273-292
8. Paul, B. Iannini, 2002. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. Pharmaceutical Biol., 1: 121-128.
9. Peter, K., C. Honig, Dale Wortham and Kaveh Zamani, 1993. Terfenadine-Ketoconazole Interaction Pharmacokinetic and Electrocardiographic Consequences. JAMA. 269: 1513-1518.

10. Pohjolan, M., Viitasalo, L. Toivonen and P. Neuvonen, 1993. Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur. J. Clin. Pharmacol., 45: 191-3.
11. Roy, M., R. Dumaine and A.M. Brown, 1996. HERG, a primary human ventricular target of the nonsedating antihistamine. Circulation, 94: 817-823.
12. Salata, J.J., N.K. Jurkiewicz; A.A. Wallace, R.F. III Stupienski, P.J. Jr.Guinosso and J.J. Jr. Lynch, 1995. Cardiac electrophysiological actions of the histamine H1 receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. Circ. Res., 76: 110-119.
13. Sousa, C.A., 1988. Atopic dermatitis. J. Small. Anim. Pract., 18: 1049-59.
14. Takahara, A., A. Sugiyama, Y. Ishida, Y. Satoh, K. Wang, Y. Nakamura and K. Hashimoto, 2006. Long-term bradycardia caused by atrioventricular block can remodel the canine heart to detect the histamine H1 blocker terfenadine-induced torsades de pointes arrhythmias. Br. J. Pharmacol., 147: 634-41.
15. Yoshihide Kii, Katsuyoshi Nakatsuji, Isamu Nose, Masafumi Yabuuchi, Michiaki Matsuda and Tsugutaka Ito, 2003. Effects of antihistamines, ebastine and terfenadine, on electrocardiogram in conscious dogs and cats,Drug Development Res., 58: 209-217.