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The Comparative Effects of Four Antihistamines on Isolated Rat Atria

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ABSTRACT

It has been reported that some of H1 receptor antagonists have important effects on cardiovascular system. Terfenadine as a non-sedative H1 receptor antagonist has an arrhythmogenic activity. In this study we have shown the effects of four antihistamine drugs: terfenadine, loratadine, clemastine and diphenhydramine, on the rate and contractions of isolated rat atria. Terfenadine (1-10 μM) caused a negative chronotropic effect (19.5-80%) and arrhythmia after 10 min. followed by a decrease in the contractile force by (7.5%), and finally after 45 min. asystolia occurred. Loratadine (30-150 μM) decreased the rate of contractions (10-82%) after 10 min. the contractile force of atria was decreased (10-19%) after 20 min. Loratadine did not produce any arrhythmia. Diphenhydramine (5-20 μM) produced bradycardia (14.5-43%) after 20 min and decreased the contractile force (2.5-40%) after 40 min. Clemastine (3-10μM) produced negative chronotropic and inotropic effect by (11.5-42%) and (10-58%) respectively. These findings indicate that all four drugs caused bradycardia and reduced contractile force, but in the case of terfenadine, it also had arrhythmogenic activity. Loratadine had the least cardiotoxic effect.

Keywords: *antihistamines, contractile force, heart rate, cardiotoxic*

Antihistamines are among the most widely used classes of drugs in modern societies [1]. These compounds are prescribed for treatment of allergies that act by blockade of specific H1 histamine receptors in skin, pulmonary, gastrointestinal, neural and cardiac tissues [2]. These classes of drugs are divided into two groups.
The first generation antihistamines were approved by the Food and Drug Administration (FDA) over a 30 year period beginning in the middle of 1940s. Because of the excellent safety record, many of these drugs are available as Over-The-Counter (OTC) medication. These "conventional" antihistamines block central as well as peripheral H1 histamine receptors and many of them also display anticholinergic effects. As a result, users of these drugs must often endure minor discomfort from side effects that include sedation, dry mouth, headache and digestive problems.

In order to minimize the above side effects, second generation antihistamines have been developed over the past 20-year period. These antihistamines including terfenadine, astemizole and loratadine, have little central activity and therefore do not typically cause the drowsiness that conventional antihistamines induce. Because of this characteristic, these newer antihistamines are often referred to as nonsedating compounds.

In more recent years however, it has become clear that some of these nonsedating antihistamines, particularly terfenadine and astemizole, produce potentially serious cardiac arrhythmias [3]. Both terfenadine and astemizole have been associated with the clinical syndrome of "torsades de pointes" [4-7], a ventricular twisting of cardiac arrhythmia characterized by a prolongation of the QT interval and the ECG wave form that can be fatal [8]. Drug-induced "torsades de pointes" in human occurs secondary to a decrease in heart rate and prolongation of the QT interval. The mechanism underlying the cardiotoxicity of terfenadine appears to be blockade of rectifying potassium channels [9]. Due to the cardiotoxicity associated with terfenadine and more recently astemizole, questions also have been raised regarding whether torsades-type arrhythmias can also occur with the newer agents such as loratadine. Although an extensive clinical database with loratadine indicates that this is not a problem, an animal model that could predict these adverse cardiovascular events is needed.

The goal of the present study were to determine and compare the effect of four antihistamines from either groups of conventional and second generation antihistamine on the isolated rat atria. In this study we measured the two parameters of rate and contractile force as well as the pattern of cardiac rhythm in the isolated rat atrium. This study was performed on four antihistamines of diphenhydramine, clemastine, terfenadine and loratadine.

MATERIALS AND METHOD

Terfenadine was generously donated from Chimidaru Company, Loratadine from Abidi Labs, Diphenhydramine from Alhavi Labs and Clemastine from Amin Labs. Spraque Dawley rats of either sexes weighing over 450-600 g were anesthetized by diethylether and exanguinated. The heart was rapidly removed, the auricle were dissected out in modified Krebs solution and suspended in isometric conditions under a tension of approximately 0.5 g. The temperature of solution was 36-37°C. After mounting, the preparation was allowed to equilibrate for 30 minutes while rate and force of spontaneous contractions were recorded isometrically with a photosensitive transducer on Beckman RS. Dynograph recorder. Solutions of drugs were prepared so that a constant volume of 0.5 ml for each dose was added to 50 ml of the bathing fluid.

Composition of the modified Krebs solution was as follows: NaCl 118 mM, KCl 4.7 mM, $CaCl_2$ 6 mM, NaH_2PO_4 1 mM, $MgCl_2$ 102 mM, $NaHCO_3$ 25mM, glucose 11.1 mM, EDTA 0.004 mM, Vitamin C 0.1 mM and pH was 7.5.

Planning of the experiment. Four antihistamine drugs were examined on rat atria. The drugs were dissolved in deionized water (except terfenadine and loratadine) at the following concentrations:

1. Terfenadine was dissolved in dimethyl sulfoxide at the concentrations of (1, 3, 6, 10 µM). Each dose was cumulatively added to the organ bath every 10 minutes.
2. Loratadine was dissolved in dimethyl sulfoxide and was prepared at the concentrations of (10, 30, 100, 150 µM).
3. Diphenhydramine and clemastine solutions were prepared at the concentrations of (2.5, 5, 10 and 20 µM) and (1, 3, 6, 10 µM) respectively. Two parameters of rate and contractile force were measured and the pattern of contractions was evaluated.

Statistical analysis. The groups of data were declared upon (mean±SEM) and analysed by the methods of Paired t-Test, Newman Keuls and repeated measured ANOVA for ($p<0.01$) and ($p<0.001$) and N=5.

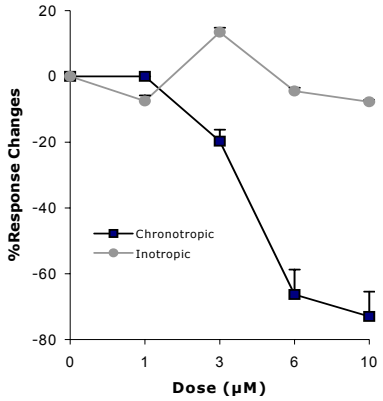

Fig 1. Effect of terfenadine (1, 3, 6, 10 µM) on chronotropic and inotropic responses of isolated rat atria.

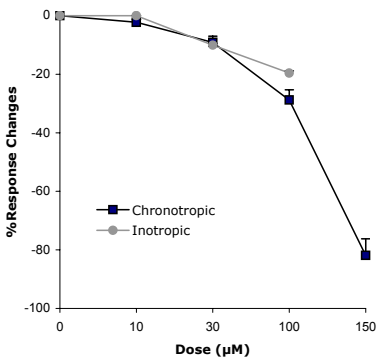

Fig 2. Effect of loratadine (10, 30, 100, 150 µM) on chronotropic and inotropic responses of isolated rat atria.

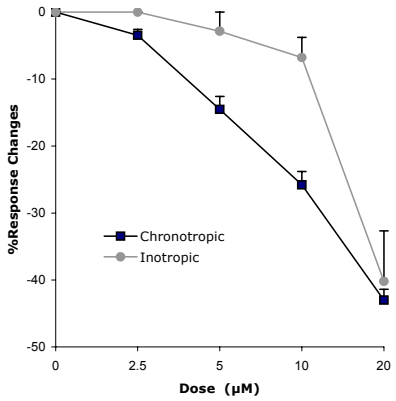

Fig 3. Effect of diphenhydramine (2.5, 5, 10, 20 µM) on chronotropic and inotropic response of isolated rat atria.

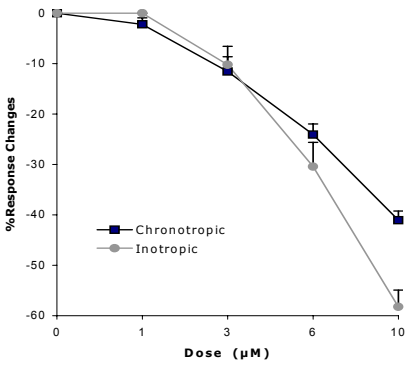

Fig 4. Effect of clemastine (1, 3, 6, 10 µM) on chronotropic and inotropic responses of isolated rat atria.

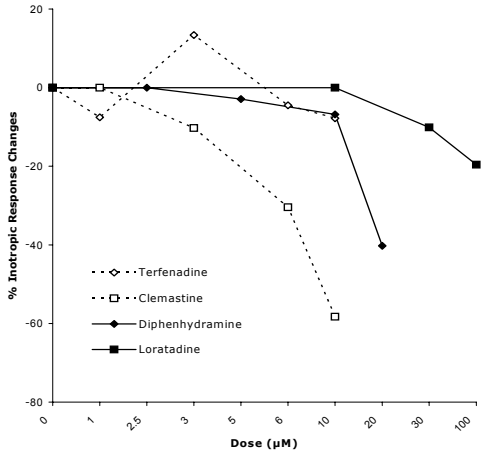

Fig 5. Dose response curve for inotropic effect of four different antihistamines: Terfenadine (3-10 µM), Clemastine (3-10 µM), Diphenhydramine (5-20 µM) and Loratadine (30-150 µM) in the isolated rat atria

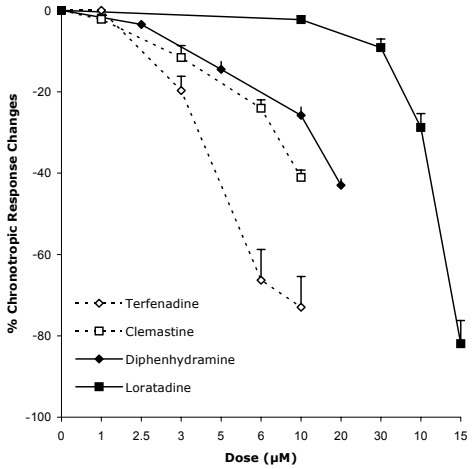

Fig 6. Dose response curve for chronotropic effect of four different antihistamines: Terfenadine (3-10 µM), Clemastine (3-10 µM), Diphenhydramine (5-20 µM) and Loratadine (30-150 µM) in the isolated rat atria

RESULTS

Terfenadine at 1-10 µM produced a negative chronotropic effect followed by severe arrhythmia (3 µM) after 10 minutes. The effect was dose-dependent and significant bradycardia was produced at 6-10 µM ($p<0.001$) leading to complete heart block (Fig. 1). Terfenadine (3 µM) also decreased contractile force (CF) of rat atria by (7%). Some positive inotropism was observed following treatment with 3 µM terfenadine, which was associated with severe arrhythmia. Terfenadine (6-10 µM) decreased the force of contractions and finally led to asystolia (Fig 1).

Loratadine at 10-30 µM produced no significant effect on CF and rate compared with control, but there was a significant concentration-dependent decrease in cardiac rate at higher concentrations (100-150 µM) ($p<0.001$).

Diphenhydramine (5-20 µM) caused a concentration-dependent bradycardia (14.5-43%) in isolated rat atria and also produced a decrement of CF at 20 µM (40%) after 40 min (Fig 3).

Clemastine (3-10 µM) produced significant bradycardia after 10 min. ($p<0.01$) in a concentration-dependent manner (Fig 4). The drug also showed a significant concentration-dependent decrease in CF (30-58%) in isolated rat atria.

The comparative effect of four antihistamines on contractile force and heart rate are also shown in Fig 5 and 6 respectively.

DISCUSSION

In this study we examined four different antihistamines, representing two major classes of H1 histamine receptor blockers for their ability to alter heart rate (HR) and contractile force (CF) in isolated rat atria. These finding indicate that all four drugs exert a depressant action upon contractile force and heart rate of isolated rat atria. Although the antihistamines tested have decreased HR and CF, some were clearly more effective at doing so than others. Clemastine was the most potent of the antihistamine tested in this study. So from the cardiotoxic aspect these compounds can be divided into 3 groups:

1. Those with potent cardio-depressant effect such as clemastine and diphenhydramine.
2. Those with potent arrhythmogenic activity such as terfenadine.
3. Those with minimal cardiotoxicity such as Loratadine.

In accordance with the study of Wang and Ebert, conventional antihistamines shared similar potency with quinidine, an antiarrhythmic drug well known for its ability to cause QT lengthening and "torsades de pointes" [12], but were not quite as potent as terfenadine. This non-sedating antihistamine also reported to cause QT prolongation [3] and "torsades de pointes" [4, 10]. Terfenadine was not very potent at prolonging QT interval. It is known to be an effective blocker of the delayed rectifier potassium channel in ventricular cardiac myocytes isolated from cat [9]. In one study, the actions of terfenadine and astemizole were directly compared with chlorpheniramine. In this study they found that astemizole was by far the most potent of these three drugs at blocking potassium current in isolated guinea-pig myocytes [11]. However they also found that terfenadine was much more potent than chlorpheniramine at blocking potassium current.

In this study the alkylamines, including diphenhydramine, which belongs to the ethanolamine class of antihistamines, showed a strong influence on cardiac repolarization. Clemastine, like diphenhydramine, contains two phenyl groups, but unlike diphenhydramine, a

chlorine atom is bound to the para carbon of one of these groups. Clemastine was the most potent conventional antihistamine tested in this study, the dual phenyl groups with a parachloro moiety may represent an important structural feature that can, in part, be used to predict whether slowing of cardiac repolarization is likely to occur [12]. These observations were consistent with our study considering the effect of clemastine on rate and contractions of isolated rat atria. The specific mechanism whereby these drugs slow cardiac repolarization also remains unidentified. Their ability to prolong the QT interval suggests that it is likely that interference with outward potassium currents is involved, although other currents have also been implicated [13]. Unlike terfenadine however, other conventional antihistamines tested in this study have not been associated with cardiac arrhythmias. Moreover because diphenhydramine and clemastine displayed greater potency at slowing cardiac rhythm than terfenadine (a drug known to be associated with "torsades de pointes" in human) [3, 9, 10], further investigations into their actions on cardiac function would be necessary.

The newer second-generation antihistamine loratadine was also examined on the rat atrial preparation. In this study loratadine (30-100 μM) significantly decreased the force of contraction of isolated rat atrium ($p<0.001$). At the higher doses (150 μM) loratadine has been associated with a cardiodepressant effect and finally atrial block. The effect of non-sedating antihistamines on potassium channels was investigated by two methods by Ducic et al (in 1997) who quantified effects of terfenadine and loratadine on Ikr currents. The major finding of their study was that terfenadine was the more effective drug in suppressing the K^+ channels. Although terfenadine generally suppressed all cardiac K^+ channels examined, the most susceptible K^+ currents were Ikr and Iped. On the other hand loratadine had little or no effect on Ikr or Iped at significantly higher concentrations than those possibly achieved in plasma [2]. Such variations between suppressive effect of terfenadine and loratadine particularly on Ikr may be responsible on the marked differences in the effects of these drugs on the QT interval, and induction of arrhythmias [14], suggesting the latter to be safer at therapeutic concentrations. As shown in this study terfenadine is very different from loratadine with respect to its effect on rate and contractions of the rat isolated atria. With regard to the mode of action of H1 receptor antagonists, these drugs have fairly diverse molecular structures, especially when considering their amino substitutes. For instance, loratadine lacks the long hydrocarbon amino tail found in terfenadine. This may, in part, contribute to the selectivity in blocking K^+ channels. Consistent with this idea, other H1-antagonists such as astemizole and ebastine, with amino tail substituent similar to terfenadine, also produced QT prolongation [15] as they suppress Ikr [11, 16]. The drugs lacking or having different types of amino substitutes, such as loratadine, show little or no QT prolongation on K^+ channels suppressive effects [9].

In conclusion our studies showed that the strongest compound on producing bradycardia was clemastine, whereas the one produced arrhythmogenic activity was terfenadine. Loratadine as shown by the other investigators [2, 17] presented insignificant effect on the isolated rat atria or adverse cardiac effect only at high doses in this investigation.

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REFERENCES

1. Du-Buske LM. Clinical comparison of histamine H1-receptor antagonist drugs. *J Allergy Clin Immunol* 1996;**98:**S307-18.
2. Ducic, CM, Shuba Y, Morad M. Comparative effects of loratadine and terfenadine on cardiac K+ channels. *J Cardiovasc Pharmacol* 1997;**30:**42-54.
3. Woosley RL. Cardiac actions of antihistamines. *Annu Rev Pharmacol Toxicol* 1996;**36:**233-252.
4. Craft TM. Torsades de pointes after astemizole overdose. *Br Med J* 1986;**292:**660.
5. Snook J, Coothman-Burrell D, Watkins J, Colin-Jones D. Torsades de pointes ventricular tachycardia associated with astemizole overdose. *Br J Clin Pract* 1988;**42:**257-259.
6. Monahen BP, Ferguson CL, Killocavy ES, Lioyd BK, Troy J, Centilena LR. Torsades de pointes occurring in association with terfenadine use. *JAMA* 1999;**264:**288-290.
7. Mac Connell TJ, Stanners AL. Torsades de pointes complicating treatment with terfenadine. *Br Med J* 1991;**302:**1469.
8. Faber TS, Zehender M, Just H. Drug- induced torsades de pointes. *Drug Saf* 1994;**11:**463-476.
9. Keren A, Tzivoni D. Ethiology, warning signs and therapy of torsades de pointes: a study of 10 patients. *Circulation* 1981;**64:**1167-1174.
10. Goodman JS, Peter CT, Mandel WJ, editors. Cardiac arrhythmias. 3rd ed. Philadelphia: JB Lippincott; 1995. p. 173-191.
11. Salata JJ, Jurkeiwicz NK, Wallace AA, Tupienski RF, Guinosso PJ, Lynch JJ. Cardiac electrophysiological actions of the histamine H1 receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. *Circ Res* 1995;**76:**110-119.
12. Wang WX, Ebert SN, Liux K, Chen YW, Drici M, Dand-Woosley RL. Conventional antihistamines slow cardiac repolarization in isolated perfused (langendorff) Feline Hearts. *J Cardiovasc Pharmacol* 1998;**32:**123-128.
13. Ming J, Nordin C. Terfenadine blocks time-dependent Ca^{++}, Na^+, and K^+ channels in guinea-pig ventricular myocytes. *J Cardiovasc Pharmacol* 1995;**26:**761-769.
14. Hey JA, Del-Prado M, Chapman RW, et al. Antihistamine activity, central nervous system and cardiovascular profiles of histamine H1 antagonists, comparative studies with loratadine, Terfenadine and sedating antihistamines in guinea-pigs. *Clin Exp Allergy* 1994;**93:**163-171.
15. Hey JA, Del-Prado M, Sherwood J, Kreutner W, Egan RW. Comparative analysis of the cardiotoxicity proclivities of second generation antihistamines in an experimental model predictive of adverse clinical ECG effects. *Drug Res* 1996;**46:**153-158.
16. Ko CM, Fan J, Mac-Cormack M, Cleeman L, Morad M. Modulation of K^+ currents by non-sedating H1-antagonist Ebastine in guinea-pig ventricular myocytes. FASEB J 1996;**10:**A316.
17. Hey JA, Del-Prado M, Egan RW, Sherwood J, KreutnerW. Loratadine produces antihistamine activity without adverse CNS, ECG or cardiovascular effects in guinea-pigs. *Int Archive Aallergy Immunol* 1995;**107:**418-419.

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