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Original Article

Reduction of cardiac effect of propranolol in lisinopril treated isolated rabbit heart

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ABSTRACT

Background; Angiotensin converting enzyme inhibitors are widely used in hypertensive patients who may come across to a condition which require emergency treatments.

Objective: Pharmacodynamic interaction of Propranolol and Lisinopril was assessed in this study with variable exposure of myocardium according to time.

Materials and methods: 20 healthy male rabbit divided in two groups were selected for the study. Lisinopril was given in a dose of 10mg/kg orally for 9 days. The effects of Propranolol were determined on isolated hearts by using Langendroff's technique.

Result: The negative ionotropic effect of Propranolol were significantly decreased ($P<0.05$).The negative chronotropic effect of low dose was significant ($P<0.05$) while at high dose the effect was insignificantly decreased ($P>0.05$).

Conclusion: The response of propranolol is reduced in lisinopril treated heart.

Keywords: Pharmacodynamic interaction, Langendroff's technique, negative ionotropic, negative chronotropic.

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INTRODUCTION

Fundamental principles of curing a patient are intrinsic to a successful approach but the most important is to have the fundamental knowledge about disease mechanism, the effect of therapeutic strategies and to forecast the outcome. However, with all the efforts sometimes the outcomes are unpredictable, due to the alteration in the tissues not only by disease process but also by the treatment. This phenomenon is more important in cardiovascular diseases in which most of the times outcome is measureable by certain parameters like blood pressure, heart rate, cardiac rhythm etc and changes in tissue receptors produce noticeable change in the outcome.

Propranolol is a non-selective blocker of beta adrenoceptor. Propranolol inhibits the activation of adenylyl cyclase and cause reduction in cardiac output, heart rate and blood pressure. It also reduces the coronary flow and myocardial oxygen consumption (1). Propranolol has received enormous clinical attention because of their efficacy in the treatment of hypertension, ischemic heart disease, congestive heart failure and certain arrhythmias (2). Angiotensin causes reflex bradycardia with intact baroreceptor reflexes and ACE inhibitors decreases the angiotensin concentration and inhibit angiotensin stimulated Ca^{++} to cardiac muscle and inhibit myocardial contractility (3). Lisinopril an ACE inhibitor may alter the density of different receptors of the body (4, 5), among them beta adrenergic receptors are especially altered (6, 7). This study represented the changes in the responses of propranolol after up or down regulation adrenergic receptor on isolated rabbit heart.

MATERIALS AND METHODS

Twenty healthy, male rabbits weighing 1000-1200 grams were selected for the study, which were divided into two groups. Both of the groups were acclimatized for housing condition, before starting the experiment. All the animals had full access of water and food *adlibitum*. One of the groups received 10mg/kg of lisinopril orally for 9 days (8). Other group was considered as control and was treated by normal saline for the same period. The animals were sacrificed and the heparinized heart was isolated as per recommended procedure (9). The nutrient and oxygen were provided by Mc Evens solution. The effect of propranolol was seen by Langendroff's technique after the up or down regulation of receptors by administration of lisinopril (10). The force of contraction i.e. the ionotropic effect were recorded as amplitude and rate of contraction i.e. chronotropic effect were recorded as no of beats.

The data was entered in SPSS version 16 (statistical package for social science) descriptive statistics was presented as mean and standard error means (SEM) based over distribution.

RESULTS

In this study the ionotropic and chronotropic effects of propranolol were observed as amplitude and rate of contraction respectively.

Table 1: Effect of Propranolol on Myocardial Contraction after chronic administration of Lisinopril (n=10)

Dose (gm)	Without Lisinopril	With Lisinopril	Significance
10^{-4}	$-34.99 \pm 2.2^{*}$	-30.81 ± 3.1	$p<0.05$
10^{-3}	-52.05 ± 2.6	-48.11 ± 2.3	$P<0.05$

* Mean ± SEM; n= No. of observation

Comparison of percentage change in amplitude after administering propranolol independently and with chronic administration of lisinopril: Contraction induced by 10^{-4} gm and 10^{-3} gm propranolol in isolated heart setup were represented **Table 1**. It was increased upto -30.81 ± 3.1 with lisinopril from -34.99 ± 2.2 without lisinopril. Propranolol at 10^{-3} gm also increased the amplitude upto -48.11 ± 2.37 with lisinopril from -52.05 ± 2.6 without lisinopril. Both the changes were statistically significant ($p<0.5$) **Fig. 1**.

Comparison of percentage change in rate of contraction after administering propranolol independently and with chronic administration of Lisinopril: The percentage change from normal in heart rate of lisinopril treated isolated heart after administration of 10^{-4}gm and 10^{-3}gm of propranolol has been given in **Table 2**. It was -6.95 ± 0.30(10) with lisinopril while the change in heart rate was -7.80 ± 0.40(10) after adding propranolol alone. The reduction of response of propranolol was statistically significant ($p<0.5$) at this dose. After adding 10^{-3} gm propranolol in lisinopril treated heart the rate of contraction was increased upto -8.98 ± 2.0(10) which was statistically insignificant ($p>0.5$) as compared to the rate observed without lisinopril, which was -10.70 ± 1.30(10) **Fig. 2**.

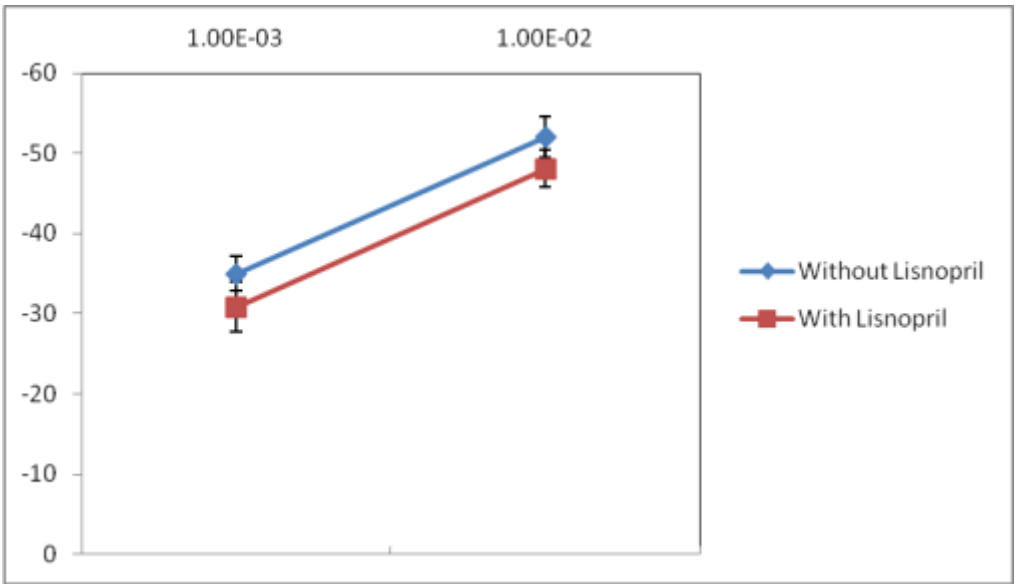

Fig.1: Comparision of effect of propranolol on amplitude after chronic administration of lisinopril.

Table 2: Effect of Propranolol on Heart rate after chronic administration of lisnopril (n=10)

Dose (gm)	Without Lisinopril	With Lisinopril	Significance
10^{-4}	-7.8 ± 0.4*	-6.92 ± 0.3	p<0.05
10^{-3}	-10.7 ± 1.3	-8.98 ± 2.0	p>0.05

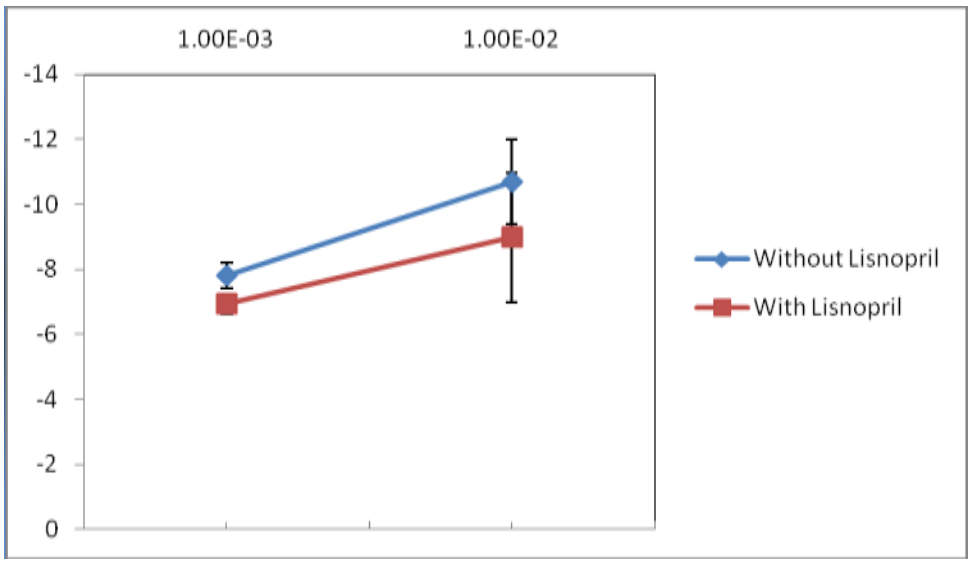

Fig 2: Comparison of effect of propranolol on heart rate after chronic administration of lisinopril.

DISCUSSION

The unpredictable responses of cardioselective drugs may be due to desensitization or up or down regulation of receptors. Several studies have documented changes in drug responsiveness cased by increased or decreased receptor sites or by alteration in the efficiency of coupling of receptors to distal effectors mechanism (11). In some cases changes in receptor number is caused by hormones, for example, thyroid hormone increase both number of receptor in the heart muscle and cardiac sensitivity to catecholamine (12). These changes contribute to tachycardia in hyperthyritoxicosis (13). The other example of down regulation of receptor is withdrawal of clonidine. Cloniodine is alpha-2 receptor agonist and used in the treatment of hypertension (14). The drug down regulates the alpha-2 receptors of brain. The phenomenon of up

or down regulation may also be seen with ACE inhibitors.

The clinical potential of this study was very high because in pharmacotherapy of cardiac patient we come across in the situation in which we require to administer certain cardioselective drugs in emergency to the patients who have received lisinopril since long. The up or down regulation cardiac receptors have been investigated by many scientist (15-17). Along with these hypotheses the ACEIs also produce cardiac remodeling and effective in the treatment of hypertrophy (18). In our study when we administered propranolol alone on isolated rabbit heart, it produces negative ionotropic and negative chronotropic effects. But the extent of ionotropism and chronotropism was decreased in lisinopril treated heart. This may be due to the desensitization of beta adrenergic receptor of heart or may be the prolong exposure of lisinopril to the heart alter the density of beta adrenergic receptor of heart. The phenomenon was reported by many researchers (19-21). It has also been reported that the response of adrenaline is also altered due to the longterm administration of lisinopril in isolated rabbit heart (22). Similarly the combination of these drugs i.e. propranolol (adrenergic antagonist) and lisinopril produce significant change in the force of contraction as well as heart rate. The response of propranolol was reduced when it is given with lisinopril as compared to the propranolol alone. The decreased antagonistic activity may be due to the down regulation of adrenergic receptors of the heart or due to the desensitization of beta adrenergic receptors.

Conclusion

At the end it is concluded that there is a dose dependent pharmacodynamic interaction between lisinopril and propranolol. Therefore significant reduction in the responses of propranolol was observed during the study. The force of contraction of lisinopril treated heart was significantly increased on both doses of propranolol while the negative chronotropic effect of propranolol was also decrease in lisinopril treated heart. Thus, before its implementation into clinical situation, to confirm this hypothesis, it is needed to explore the study by using more sophisticated techniques that actually determine the adrenergic receptor density.

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