REPORT

Study of alteration of adrenergic receptor response by chronic use of lisinopril: An ACE inhibitor

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Abstract: Unpredictable outcomes of life saving drugs have been seen in patients who receive different cardioselective drugs for longer periods. Many studies have been conducted to explore these responses. This study shows the down regulation of adrenergic receptors due to chronic use of Lisinopril, an ACE inhibitor as a cause of poor response of adrenaline. Langendroff's technique was used. The data obtained from ten rabbits shows that effective dose of Lisinopril (10mg/kg daily orally) reduces the inotropic and chronotropic effects of adrenaline significantly ($p<0.05$).Therefore it is suggested to use higher doses of adrenaline in cardiac units in patients who have used therapeutic doses of Lisinopril for longer periods provided it is supported by clinical studies.

Keywords: Cardio selective, up or down regulation, Lisinopril, Langendroff's technique.

INTRODUCTION

The receptors in cardiovascular system involve in a variety of controls such as contractile force, circulatory adjustment and perfusion of tissues. The study of drug receptor activity provides the basis for understanding of these actions and evolves guidance for the clinical use of drugs.

β_1 receptors are responsible for numerous functional responses including heart rate, contractility, automaticity, excitability and force of contraction of cardiac muscles (Westfall, 2006). β_2 adrenergic receptors are concentrated mainly in ventricle and atria, where they are similarly coupled to myocardium contractile system (Bristow *et al.,* 1986). β_3 adrenoceptor are mainly located in coronary vascular bed (Stroberg, 1995). Effects of many cardioselective drugs may be altered due to the up or down regulation of the receptors that has been proved. For example; β adrenergic blockers can produce withdrawal syndrome on sudden discontinuation that reminiscent of sympathetic hyperactivity. Rebound hypertension to level higher than those that existed before treatment has been noted with discontinuation of β antagonist in hypertensive patient (Houstan and Hodge, 1988), which may perhaps be due to changes of β receptors. The up or down regulation of various receptors may also be seen in other tissues, for example, the acute administration of sulfonylurea increases insulin release from the pancreas but chronic administration declines the circulatory insulin levels. This is due to down regulation of receptors situated at cell surface for sulfonylurea on the pancreatic β-cells (Davis and Granner 2001). Lisinopril an ACE inhibitor provides another example; it is an orally active inhibitor of peptidyldipeptide hydrolyses, which inhibits the conversion of angiotensin I into angiotensin II. Since ACE inhibitors increase bradykinin so prostaglandin synthesis is stimulated so an acute reduction in blood pressure is observed (Gainer *et al,* 1998).Various studies have proved the alteration in the microscopy of the β receptors by ACE inhibitors (Graf *et al.,* 2003). However our study represents the changes in responses of adrenaline after up or down regulation of adrenergic receptors.

MATERIALS AND METHODS

Ten 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. Other group was considered as control and was treated by placebo for the same dose and period. The effect of adrenaline was seen by Langendroff's (1895) technique after the up or down regulation of receptors by chronic administration of Lisinopril.

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.

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RESULTS

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

The mean value shows that after administration of 10^{-4} gm of adrenaline, the amplitude was increased to 40.21 ± 6.3 (5) and the rate was 40.05 ± 3.7 (5) from normal, while at 10^{-3} gm of adrenaline the amplitude was 42.59 ± 6.7 (5) and the rate was 44.68 ± 5.4 (5) as compared to zero dose. The percentage changes in amplitude and rate induced by adrenaline (10^{-4}gm) after treating with 10mg/kg of Lisinopril for 9 days was 36.87 ± 5.2 (5) and 41.03 ± 3.6 (5) respectively. At 10^{-3} gm of adrenaline the amplitude was 37.81 ± 6.10 (5) and rate was of 41.07 ± 3.53 (5) in Lisinopril treated heart.

Table I depicts the comparison of percentage change in amplitude after administering adrenaline with or without Lisinopril. The amplitude in Lisinopril treated isolated heart at 10^{-4} gm adrenaline was decreased significantly ($p<0.05$), as compared to amplitude of adrenaline without Lisinopril. The amplitude at 10^{-3}gm of adrenaline in chronic Lisinopril treated heart was also significantly decreased ($p<0.05$), as compared to adrenaline alone.

Table II shows the comparison of percentage change in rate after administering adrenaline with or without Lisinopril. The heart rate was increased which is statistically significant ($p<0.05$) as compared to rate increased by adrenaline without Lisinopril. At 10^{-3}gm of adrenaline with Lisinopril, the change in the rate of contraction was statistically not significant ($p>0.05$) as compared to rate with adrenaline alone in isolated rabbit heart.

DISCUSSION

A powerful stimulant effect on heart is exerted by catecholamine, through β_1 adrenoceptors. Both heart rate and force of contraction are increased, resulting in a markedly increased cardiac output and cardiac oxygen consumption. Catecholamine can also cause disturbance of cardiac rhythm (Rang *et al.,* 2003). This may be important in pathophysiology of hypertension and cardiac failure. It causes reflex bradycardia with intact baron receptor reflexes.

ACE inhibitors decrease the angiotensin concentration and inhibit angiotensin stimulated Ca^{++} to the cardiac muscles and inhibit the myocardial contractility (Cassis, 1997).

We explored the responses of adrenaline on the isolated rabbit's heart, which received Lisinopril in certain dose for a long period exogenously.

This study has high potential as in the treatment of cardiac patients. We come across in situations in which we require to administer a cardioseletive drug in the patients who have received Lisinopril since long. Several hypotheses have been postulated for the up or down regulation of cardiac receptors upon the administration of cardioselective drugs (AlexenderNap *et al.,* 2003, Makino. *et al.,* 2003, Ishyama *et al.,* 2004, Igase *et al.,* 2008). Along with these hypotheses the ACEIs also produce cardiac remodeling and effective in the treatment of cardiac hypertrophy which was also proved by many scientists. In our study when we administered adrenaline alone on isolated rabbit heart it produces positive inotropic and positive chronotrapic effects, but this inotropism is decreased with chronic administration of Lisinopril. This may be due to down regulation of β_1 adrenoceptors of heart or may be due to prolonged exposure of Lisinopril to the heart. It is supported by many direct (Graf *et al.,* 2003) and indirect evidences in literature (Akashi *et al.,* 2000, Alexander Nap *et al.,* 2003, De Tommasi *et al.,* 2003). ACE inhibitor reduces the angiotensin II level and decreases the angiotension II stimulated cardiac contractility via opening of voltage gated Ca^{++} channels and increased heart rate via increased sympathetic tone (Jackson, 2006). Whereas normally adrenaline causes increased cardiac contraction via opening of Ca^{++} channels and increased inward movement of Ca^{++} (Rang *et al.,* 2003). The combination of both of

Table 1: Comparison of percentage changes in force of cardiac contraction after adrenaline (n=5)

Dose (mg)	Without Lisinopril	With Lisinopril	Significance
10^{-4}	40.21 ± 6.3*	36.87 ± 5.2	$p<0.05$
10^{-3}	42.59 ± 6.7	37.81 ± 6.1	$p<0.05$

* Mean ± SEM

Table 2: Comparison of percentage change in rate of cardiac contraction after adrenaline (n=5)

Dose (mg)	Without Lisinopril	With Lisinopril	Significance
10^{-4}	40.05 ± 3.7*	41.03 ± 3.6	$p<0.05$
10^{-3}	44.68 ± 5.4	41.07 ± 3.5	$p>0.05$

* Mean ± SEM

these drugs i.e. Lisinopril and adrenaline produced significant decrease in the force of contraction but rate was increased after combining these drugs. Response of the adrenaline was reduced, when they are given with Lisinopril as compared to the effect produced by the drug alone. This decreased agonistic activity of catecholamine may be due to down regulation of beta receptors in heart. The changes in β-receptors activity were observed which is supported by data and literature.

Our data provides a clear cut indication to use relatively higher doses of adrenaline in patients who have used Lisinopril or perhaps other ACE inhibitors for longer periods if it is supported by clinical studies.

CONCLUSION

It is concluded that significant effect of prolonged Lisinopril administration was seen on β-receptors. Therefore, the response of adrenaline was changed after prolong treatment by Lisinopril. Adrenaline does not improve the heart rate and force of contraction so much in the heart which has already received Lisinopril for prolong period. So to evaluate the further responses it is needed to extend the study and to use more sophisticated techniques to determine the receptor alteration.

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