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ORIGINAL ARTICLE

Effect of Cardioselective Beta Blocker on Lisinopril Treated Isolated Rabbit's Heart

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ABSTRACT

***Background*:** Certain drugs produce unpredictable responses when used in emergency conditions. These variable outcomes may be harmful or beneficial for the patient.

***Objective*:** This study has been conducted to evaluate the pharmacodynamic interaction between angiotensin converting enzyme inhibitor and metoprolol, a selective blocker of β_1 receptors. Cardioselective beta blockers are commonly used to treat hypertension, arrhythmias and ischemic heart disease.

***Method*:** In this study, 20 healthy male rabbits were selected and divided into two groups. Effective dose of Lisinopril (10 mg/kg) was administered orally *via* oral feeding, for 9 days. By using Langendroff's technique, the effects of metoprolol were observed in isolated hearts.

***Result*:** The data showed that the effective dose of Lisinopril (10 mg/kg daily orally) increases the inotropic and chronotropic effects of metoprolol significantly ($p<0.05$).

***Conclusion*:** Therefore, lisinopril, an inhibitor of angiotensin converting enzyme may increase the response of cardioselective beta blocker metoprolol in isolated rabbit's heart.

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

INTRODUCTION

Metoprolol is a selective β_1-receptor antagonist that acts through deactivation of adenylyl cyclase. These antagonists thus affect various cardiovascular events by reducing cardiac output, coronary flow, heart rate, and blood pressure while improving the myocardial oxygen consumption. They also cause reduction a in arterial blood pressure by reducing cardiac output and decrease rennin release from the juxtaglomerular cells of kidney. The β_1-adrenoceptor antagonist has an antiarrhythmic effect on heart mainly by increasing the refractory period of AV node [1].

ACE inhibitors, Lisinopril decrease angiotensin concentration in the blood which decreases the angiotensin dependent Ca^{++} ion concentration in cardiac muscle and thus inhibits myocardial contractility. With intact baroreceptor activity, angiotensin also causes reflex bradycardia. ACE inhibitors also decrease vascular permeability of endothelium in large arteries and decrease spaces in the aorta, coronary artery and peripheral arteries [2]. These are the general effects of individual drugs but when these drugs are administered concomitantly, they may affect the responses of each other [3-5]. In this study the response of a cardioselective drug

metoprolol in lisinopril treated isolated rabbits heart has been explored. This study has great clinical importance for cardiac patients who have a history of prolonged use of lisinopril and also need to administered another cardioselective drug specially metoprolol.

MATERIALS AND METHODS

Animal Selection

In this study, ten healthy male rabbits weighing 1 kg to 1.2 kg has been selected. Each animal was kept in separate cage under controlled climatic condition during entire study in an alternating 12 hours light and dark cycle. All animals had full access to water and standard laboratory food *ad libitum*. All the animals have been divided into two groups, each comprised of five animals. The nutrient and oxygen were provided by McEwens solution.

Ethical Approval

The study was approved by the Ethical Committee of Baqai Medical University. All the animals were housed under controlled environment in the animal house of Baqai Medical University, Karachi.

Drug Administration

First group was treated with normal saline with similar dose and time period and served as control while the second group treated with lisinopril (10 mg/kg, 9 days). After 24 hours of the last dose, all animals have been sacrificed and their hearts were isolated according to the designed protocol for further study [6-8].

Effect of Drug on Isolated Heart

Langendroff technique [9] has been used to observe the effect of metoprolol after the administration of lisinopril causing up or down regulation of the receptors. In Langendroff technique, isolated heart was incorporated with aorta, to measure various cardiac responses like heart rate, force of contraction, coronary blood flow and cardiac tissue stimulations, *etc*. The basic principle is to maintain cardiac activity by perfusing the heart *via* the coronary arteries using an aortic cannula inserted into the ascending aorta. Perfusion solution is delivered to the heart in a retrograde manner *via* this cannula.

Statistical Analysis

The data were treated with the Statistical Package for Social Science version 16 and the descriptive statistics were presented based on the distribution to calculate mean and standard error mean (SEM).

RESULTS

The effect of metoprolol on force and rate of cardiac contraction in terms of amplitude (measured as length of beats) and rate of contraction, respectively has been observed in this study.

Assessment of Metoprolol Effect on Isolated Rabbit Heart

Administration of 0.1 mg and 1 mg of metoprolol showed the percentage changes in rate and amplitude from normal (Table **1**). The mean values of amplitude at dose 0.1 mg of metoprolol was found as -11.63 ± 1.2 and rate was -21.14 ± 1.7, while at dose 1 mg the amplitude was further decreased to -20.01 ± 2.7 and rate was -29.41 ± 2.3 as compared to normal.

Table 1. Effect of metoprolol on isolated rabbit heart.

Dose	Percentage Change	
	Force of Contraction	Rate^{+}
0.1 mg	-11.63 ± 1.2*	-21.14 ± 1.7
1 mg	-20.01 ± 2.7	-29.41 ± 2.3

* Mean ± SEM; + = No. of beats/min; n = No. of observation; (n=5)

Table 2. Effect of metoprolol on isolated rabbit heart after treatment of lisinopril.

Dose	Percentage Change	
	Force of Contraction	Rate^{+}
0.1 mg	-11.98 ± 1.7*	-22.43 ± 1.6
1 mg	-23.05 ± 2.6	-29.99 ± 2.2

* Mean ± SEM; + = No. of beats/min; n = No. of observation; (n=5)

Evaluation of Effect of Metoprolol on Isolated Rabbit Heart After Treatment of Lisinopril

The changes in percentage of amplitude and rate after administration of lisinopril are given in Table **2** and then treated with two doses of metoprolol. The mean values observed for the force of contraction which decreased upto -11.98 ± 1.7 and similarly rate was decreased upto -22.43 ± 1.6 while amplitude and

rate after 1 mg of metoprolol was further decreased upto -23.05 ± 2.5 and -29.99 ± 2.2, respectively after the treatment of lisinopril.

Comparison of Effect of Metoprolol on Amplitude, Individually and with Treatment of Lisinopril

The effect of metoprolol (0.1 mg and 1 mg) were given in Table **3** when administered with the treatment of lisinopril shown a decrease in the amplitude upto -11.98 ± 1.7 shows statistical significance ($p<0.05$) as compared to the amplitude calculated in response to metoprolol alone *i.e*. -11.63 ± 1.2. The amplitude at 1 mg of metoprolol with lisinopril was further found to be decreased as -23.05 ± 2.6 with statistical significance of $p<0.05$ as compared with metoprolol independently *i.e*. -20.01 ± 2.

Table 3. Comparison of effect of metoprolol on amplitude after administration of lisinopril.

Dose	Metoprolol Alone	Metoprolol with Lisinopril	Significance
0.1 mg	-11.63 ± 1.2*	-11.98 ± 1.7	p <0.05
1 mg	-20.01 ± 2.7	-23.05 ± 2.6	p <0.05

* Mean ± SEM; + = No. of beats/min; n = No. of observation; (n=5)

Table 4. Comparison of effect of metoprolol on rate after chronic administration of lisinopril.

Dose	Metoprolol Alone	Metoprolol with Lisinopril	Significance
0.1 mg	-21.14± 1.7*	-22.43 ± 1.6	p <0.05
1 mg	-29.41 ± 2.3	-29.99 ± 2.2	p >0.05

* Mean ± SEM; + = No. of beats/min; n = No. of observation; (n=5)

Comparison of Effect of Metoprolol on Rate Individually and with Treatment of Lisinopril

Table **4** compares the mean values observed on rate after administration of metoprolol with or without lisinopril. The rate was decreased upto -22.43 ± 1.6 when 0.1 mg metoprolol administered to the isolated rabbit heart with lisinopril having statistical significance of ($p<0.05$), while the rate was observed as -21.14 ± 1.7 in case of metoprolol alone. At 1 mg of metoprolol and lisinopril the rate was -29.99 ± 2.2 which is statistically insignificant when compared to the rate after independent administration of metoprolol *i.e*. -29.41 ± 2.3.

DISCUSSION

A physician required the predication of responses when multiple drug administered to the patients but sometimes the outcomes of these combination are totally or to the large extent different. Several studies have been carried out which prove the variation in cardiac receptor density after the administration of cardio selective drugs [5, 10, 11].

It was also investigated that in congestive heart failure ACE inhibitor along with β receptor antagonist restore low and high frequency harmonic oscillations in muscle sympathetic nerve activity [12, 13] which was exerting beneficial effects on sudden death and disease progression in congestive heart failure and this combination is also very helpful in improving left ventricular dysfunctions [14, 15]. It was also reported by many researchers that ACE inhibitors along with the beta-blockers produces a synergistic responses on cardiac remodeling or dilated cardiomyopathy [16-18]. It was also reported that variations in the sympathetic derive observed in cardiac failure. In these types of observation physician may sometimes prescribe Beta blocker to reduces the cardiac effects of epinephrine [19, 20]. Many clinical trials are also conducted to prove the additive role of beta-blockers with ACE inhibitors [21].

In this study it was investigated that altered responses of metoprolol on lisinopril treated heart. Chronic administration of lisinopril improves the β receptor density in the heart. Previous studies have been conducted by Mallem *et al*., Sethi *et al*., De Tommasi *et al*., Gilbert and Port, Akashi *et al*., and Bristow *et al*. also support this concept [22-27] and hence proved by our data. The force of contraction of cardiac muscles and heart rate both are decreased by chronic administration of lisinopril and then metoprolol *i.e*. more ionotropism and choronotropism seen when metoprolol administered to lisinopril treated heart. In other words, we can say that lisinopril increase the response of cardioselective beta blocker metoprolol.

CONCLUSION

Therefore, lisinopril, an inhibitor of angiotensin converting enzyme may increase the response of cardioselective beta blocker metoprolol in isolated rabbit's heart. These types of altered responses that are produced by ACE inhibitors are especially considerable in the emergency treatment of CHF in which ACE inhibitors are the drug of choice for long term treatment of disease and metoprolol was also administered to improve heart rate. There is a further need to explore the use of more advanced and sophisticated techniques to estimate further responses and also to evaluate the receptor density.

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