Original Paper

Role of Carvedilol in Prevention of Adrenaline Induced Myocardial Infraction in Experimental Animal

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Abstract

Introduction: Acute myocardial infarction (AMI) is the most important form of ischemic heart disease (IHD). Coronary artery disease (CAD) is an increasingly important medical and public health problem and is the leading cause of mortality in Bangladesh. AMI is the rapid development of myocardial necrosis caused by a critical imbalance between the oxygen supply and demand of the myocardium. Total occlusion of the coronary arteries for more than 4-6 hrs results in irreversible myocardial necrosis, but reperfusion within this period can salvage the myocardium and reduce morbidity and mortality.

Objectives: To assess the role of carvedilol in prevention of adrenaline induced cardiac damage in experimental animal.

Materials and Methods: This experimental study was carried out in the department of pharmacology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for a period of One year spanning from July 2004 to June 2005. Fifty two healthy rats of Long Evan Norwegian strains, 3-4 months of ages of both sexes, weight between 180-220g were used. The experiment was divided into two parts: Part-I and Part-II. Thirty two rats were selected for Part-I experiment and subdivided into Group-I and Group-II. In Part-II experiment, 20 rats were selected and placed as Group-III. Group-I (12 rats) of control group was treated with 02 doses of inj distilled water (D/W) subcutaneously (S.C.) 24 hrs apart and serum creatine kinase-MB (CK-MB) level and hepatic and cardiac reduced glutathione (GSH) contents were estimated from 06 (Group-Ia) rats after 12 hrs and serum aspartate aminotransferase (AST) level and hepatic and cardiac reduced GSH contents were estimated from 06 (Group-Ib) rats after 24 hrs of 2nd inj of D/W. Group-II (20 rats) was treated with 02 doses of inj adrenaline (2mg/kg) S.C. in 24 hrs interval and in above mentioned way serum CK-MB level, GSH (hepatic and cardiac) contents and serum AST and GSH (hepatic and cardiac) contents were estimated 12 hrs and 24 hrs after the 2nd inj of adrenaline respectively. In experimental group (Group-III) all the rats (20) were treated with carvedilol (1 mg/kg) orally for 14 consecutive days and then were given 02 doses of inj adrenaline with the interval of 24 hrs and again serum CK-MB level and GSH (hepatic and cardiac) contents were estimated from half of the rats (10) after 12 hrs of injection and serum AST level and GSH (hepatic and cardiac) contents were measured from half of the rats (10) after 24 hrs of 2nd injection of adrenaline.

Results: Adrenaline (2mg/kg) induced myocardial damage was evaluated biochemically by significant ($P<0.001$) increase in CK-MB and AST levels. Free radical production following adrenaline induced myocardial damage was reflected by significant ($P<0.001$) depletion in hepatic and cardiac reduced glutathione (GSH) contents. Cardio-protection provided by carvedilol pretreatment in adrenaline induced myocardial infarction was assessed by significant prevention of increase in serum CK-MB and AST levels. Antioxidant property of carvedilol was evaluated by significant ($P<0.001$) prevention of depletion in hepatic and cardiac GSH contents. The results of the study indicated that carvedilol pretreatment provided effective prevention in adrenaline induced myocardial damage and also provided effective antioxidative action.

Conclusion: This study indicated that adrenaline administration induced myocardial damage as evidenced by increase in serum CK-MB and AST levels which was associated with free radical production as reflected by depletion in hepatic and cardiac GSH contents. It was observed that carvedilol through their antioxidant property in addition to their β-blocking effect prevents free radical mediated injury of catecholamine assault following MI.

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Key-words: Acute myocardial infarction, coronary arterial disease, adrenaline induced cardiac damage, carvedilol, reduced glutathione (GSH).

Introduction

Acute myocardial infarction is a common disease with serious consequences in mortality, morbidity and cost to the society[1]. Acute coronary occlusion is the leading cause of morbidity and mortality in the western world and according to the World Health Organization (WHO)[2] will be the major cause of death in the world as a whole by the year 2020. CAD is highly prevedent in Bangladesh. CAD is an important medical and public health issue because it is common and leading cause of death throughout the world. The overall mortality rate has been decreased significantly over the last couple of decades. Of all south Asian countries, Bangladesh probably has the highest rates of CAD and yet is the least studied[3]. New treatment will continue to emerge, but the greatest challenges will be to effectively implement preventive actions in all high-risk individuals and to expand delivery of acute treatment in a timely fashion for all eligible patients. There is an urgent need for effective forms of secondary prevention and in particular, treatments which will limit the extent of an evolving MI during the acute phase of coronary occlusion[4]. Prevalence study in Bangladesh is few. Bangladesh has been experiencing epidemiological transition from communicable disease to non communicable disease. The pattern of CADs for a period of 1992-1997 in SSMCH, Dhaka was studied. It was concluded that all types of cardiac diseases are found in Bangladesh. About 50% of the total admissions in the cardiology unit were of coronary artery disease with male predominating and male female ratio was 3.9:1[3].

AMI causes a detectable rise in plasma concentration of enzymes which are normally concentrated within cardiac cells. The enzymes most widely used in the detection of MI are Troponin T and I, Creatine kinase (CK), Aspertate aminotransferase (AST) and Lactate dehydrogenase (LDH). Most sensitive and cardiospecific enzymes are CK-MB and Troponin T and I. Serum CK-MB reaches its peak at 12-14 hours of onset of AMI[5]. Serum AST level in patients with AMI rose to levels 2 to 20 times normal within 24 hrs of onset of AMI and returned to normal range within 3 to 6 days thereafter[6].

Reactive oxygen-centered free radicals are generated in hearts during cardiac ischemia and that a burst of oxygen radical generation occurs within moments of reperfusion[7]. Sudden presence of oxygen during reperfusion after a period of ischemia may be toxic for the myocardial cell. The myocardium also has a series of defense mechanism including the enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase and other endogenous antioxidants such as vitamin E(vit E), vitamin C (vit C) and cysteine to protect the cell against the cytotoxic oxygen metabolites. In ischemia and reperfusion, oxidative stress may occur as shown by tissue accumulation and release of oxidized glutathione (GSSG)[8]. The glutathione status (GSH/GSSG ratio) is a good indicator of oxidative stress[9]. Reduced glutathione (GSH), a tripeptide, occurs in high concentration in virtually all mammalian cells; most prevalently as intracellular thiol. GSH has many diverse functions; one is to give protection against oxidative damage. Tissue (hepatic and cardiac) GSH contents depletion is an indicator of increased toxicity including myocardial ischemia and hepatotoxicity[10]. Significant rise in the serum levels of CK-MB, AST and LDH indicate acute cardiac toxicity and markedly reduced level of cardiac or hepatic GSH contents indicates cardiac ischemic and reperfusion injury[11].

Human ventricular myocardium contains both β_1 and β_2 adrenoceptors[12]. Stimulation of β_1 adrenoceptors in the heart by endogenous catecholamines (adrenaline, noradrenaline) increase myocardial oxygen consumption which can aggravate the ischemic process. β-blockers decrease myocardial oxygen requirements by reducing myocardial contractility, heart rate and systemic arterial pressure, making them useful for treating ischemia[13]. Elevated circulating catecholamines (adrenaline and noradrenaline) in the early phase of MI raise the oxygen requirements of myocardium (by acting on β_1-adrenoceptor in the heart). Free oxygen radicals are also increased following MI. Circulating adrenaline which is increased following MI acts on presynaptic β_2-adrenoceptor and causes further release of noradrenaline. This noradrenaline further aggravates the ischemic process[14]. Prophylactic treatment with nonselective β-blocker may reduce the presynaptic β_2-adrenoceptor mediated release of noradrenaline as well as decrease oxygen requirement of myocardium by blocking β_1-adrenoceptor of the heart[15].

Cardioprotection may be defined as prevention of cardiac death and/or cardiac damage[16]. The mode of cardioprotection of β-blocker is to reduce myocardial workload, and hence oxygen demand, through reduction in heart rate and blood pressure. Moreover, in the ischaemic heart β-blockade can reduce the effect of catecholamines and can produce a favorable redistribution of blood flow[17]. Carvedilol is a unique multiple action drugs, a nonselective ß-blocker with additional vasodilating properties, caused by α_1-adrenoceptor blocked. Carvedilol significantly limits infarct size in animal models of AMI.

Carvedilol also has the potential to reduce ischaemic events and mortality. Carvedilol is well tolerated and safe to use in patients immediately after AMI[18]. Carvedilol limits myocardial necrosis resulting from coronary artery occlusion and reperfusion in a more pronounced manner than propranolol. Carvedilol would provide a greater reduction in the extent of myocardial injury following ischaemia and reperfusion than that provided by propanolol (non selective β-blocker) alone. It is anticipated that carvedilol, not other β-blockers (e.g. propranolol) would further lower myocardial O_2 demand due to α_1-blockade and calcium channel blockade[19]. The highly beneficial cardioprotective effect of carvedilol could be due to simultaneous blockade of α and β adrenoceptors; since propranolol only could block β adrenoceptor and provided less protection of the ischaemic and reperfused myocadium in the rat[20].

Some experimental studies indicated that carvedilol provides significant cardioprotection in animal models of AMI, carvedilol as a result of the carbazol moiety, is a potent andioxidant. Carvedilol and several of its metabolites inhibit lipid peroxidation, scavenge oxygen free radicals, inhibit the formation of reactive oxygen radicals and prevent the depletion of endogenous antioxidants, such as, vit E and GSH. Carvedilol reduced infarct size in rat ischemia model the other actions of carvedilol provide additional cardioprotection beyond that afforded by β-blocking effect of carvedilol. Carvedilol provided cardioprotection through β-blockade, α-blockade, calcium channel blockade and antioxidant activity[21]. Carvedilol exerted antioxidant effect by preventing depletion of hepatic and cardiac GSH contents[22]. In a comparative clinical study it was showed that carvedilol exerted more cardioprotection than labetalol[23]. It was believed to be due to α_1, β_1 and β_2 adrenoceptors blockade effects of carvedilol and antiperoxidative property of carvedilol. In some studies it was concluded that carvedilol provided greater benefit than traditional β-blockers in cardioprotection because of its antioxidant actions that synergize with its non selective β-blocking and α-blocking effects[24].

In BSMMU laboratory experimental MI in rats was induced by injecting adrenaline subcutaneously 2mg/kg body weight, two injections given 24 hrs apart[25,26]. In some studies myocardial damage was assessed by increased enzyme (CK-MB, AST and LDH) levels as well as histopathological changes[25-28]. The animal model of experimental MI can be used to study the cardioprotective effect of drugs. Therefore, the present study aims at demonstrating the cardioprotective role and the antiperoxidative property of carvedilol (both α and β-blocker) following experimentally induced MI.

Materials and Methods

This experimental study was carried out in the department of pharmacology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, during the period from July 2004 to June 2005. Fifty two healthy rats of Long Evan Norwegian strains, 3-4 months of ages of both sexes, weighed between 180-220 g were used and were obtained from the animal house of BSMMU. They were kept in standard sized metalic cages (3 rats/cage) in a well-ventilated room at room temperature with 12 hrs of light and 12 hrs dark schedules, fed normal rat diet and given water with libitum. Cardio-protective effect and antiperoxidative action was assessed by measuring the serum enzymes (CK-MB and AST) released from necrotic myocardial tissues and the hepatic and cardiac reduced glutathione (GSH) contents in experimentally induced myocardial infarction respectively.

Drugs and Chemicals: Carvedilol was supplied by Incepta Pharmaceuticals as a gift. Adrenaline, CK-MB Kit, GOT-AST Kit, Protein estimation kit, Chloroform ($CHCl_3$), Absolute alcohol, Chemicals and reagents used for determination of glutathione content, Tyrode's (physiological) solution, Distilled water etc were purchased from local market.

Experimental Design (Table–I and II): The experiment was divided into two parts, Part-I and Part-II.

PART-I Experiment (Table-I) was carried out to demonstrate the effect of adrenaline on serum CK-MB, AST levels and hepatic and cardiac GSH contents. For this purpose 32 rats were selected into two groups, such as, Group-I and II.

Group-I was served as control and consisted of 12 rats. They received vehicle i.e. 1 ml of distilled water (D/W) S.C. for two consecutive days in 24 hrs apart. This group was again divided into two sub-groups. Group-Ia was consisted of 6 rats. This group was taken for estimation of serum CK-MB and GSH contents (hepatic and cardiac) 12 hrs after the 2nd injection of vehicle. Group-Ib was consisted of 6 rats. Serum AST level and GSH contents (hepatic and cardiac) were measured in this group of animals 24 hrs after the 2nd injection of vehicle.

Group-II consisted of 20 rats. They received inj Adrenaline at a dose of 2 mg/kg body weight subcutaneously for 2 consecutive days in 24 hrs apart. This group served as experimental group and this group was again divided into two sub groups. Group-IIa consisted of 10 rats. This group was taken for estimation of serum CK-MB level and GSH contents (hepatic and cardiac) 12 hrs after the 2nd injection

of adrenaline. Group-IIb consisted of 10 rats. This group was taken for estimation of Serum AST level and GSH contents (hepatic and cardiac) after the 2nd injection of adrenaline.

PART-II Experiment (Table-II) was done to demonstrate the effect of pretreatment of carvedilol on serum enzymes (CK-MB and AST) and GSH contents (hepatic and cardiac) on adrenaline treated rats. For this purpose 20 rats were taken in Group-III and again divided into two subgroups, such as, Group-IIIa and Group-IIIb. There were 10 rats in each subgroup and total 20 rats were selected in Group-III. Rats of both groups received carvedilol at a dose of 1mg/kg body weight, 1 ml containing 200 microgram orally daily through Ryles tube (size 5G) for 14 consecutive days starting from the 1st day of experiment. On the 15th day they received 1st injection of adrenaline at a dose of 2 mg/kg body weight subcutaneously and after 24 hours 2nd injection of adrenaline was given. Group-IIIa (10 rats) was taken for estimation of serum CK-MB level and hepatic and cardiac GSH contents 12 hrs after the 2nd injection of adrenaline. Serum AST level and GSH contents (hepatic and cardiac) were estimated in 10 rats of Group-IIIb, 24 hrs after the 2nd injection of adrenaline.

All rats in all subgroups were sacrificed 24 hrs after the last dose of adrenaline under light anaesthesia. Statistical analyses were carried out using computer based programme Statistical Package for Social Science (SPSS) for windows version 10. Data obtained from the findings of the above experiments were analysed by student,s unpaired 't' test. The difference between groups was considered highly significant at P<0.001. The results were presented in a tablulated form.

Table-I: Showing the experimental design (Part-I) (n=32)

Group	Sub Group	No of Rats	Treatment Schedule	Sacrificing Schedule	Parameter Studied
I	I(a)	6	Distilled water 1 ml S.C. (1st Inj on the 1st day of experiment. 2nd inj after 24 hours)	12 hrs. after 2nd injection	CK-MB GSH contents (hepatic and cardiac)
	I(b)	6	Distilled water 1 ml S.C. (1st Inj on the 1st day of experiment. 2nd inj after 24 hours)	24 hrs after 2nd injection	AST GSH contents (hepatic and cardiac)
II	II(a)	10	Injection Adrenaline 2mg/kg S.C. (1st inj on the 1st day of experiment. 2nd inj after 24 hours)	12 hrs after 2nd injection	CK-MB GSH contents (hepatic and cardiac)
	II(b)	10	Injection Adrenaline 2mg/kg S.C. (1st inj on the 1st day of experiment. 2nd inj after 24 hours)	24 hrs after 2nd injection	AST GSH contents (hepatic and cardiac)

Table-II: Showing the experimental design (Part-II) (n=20)

Group	Sub Group	No of Rats	Treatment Schedule	Sacrificing Schedule	Parameter Studied
III	III(a)	10	Carvedilol 1mg/kg, 1ml orally (daily for 14 consecutive days) + Inj Adrenaline 2mg/kg S.C (1st injection adrenaline on 15th day and 2nd Injection after 24 hrs	12 hrs after 2nd injection	CK-MB GSH contents (hepatic and cardiac)
	III(b)	10	Carvedilol 1mg/kg, 1ml orally (daily for 14 consecutive days) + Inj Adrenaline 2mg/kg S.C (1st injection adrenaline on 15th day and 2nd Injection after 24 hrs	24 hrs after 2nd injection	ASTGSH contents (hepatic and cardiac)

Results

Part-I experiment was carried out to demonstrate the effect of adrenaline on serum CK-MB and AST levels and hepatic and cardiac GSH contents. In Table-III, it was shown that serum CK-MB level in adrenaline treated rats, Group (Group-IIa) was markedly increased as compared to control group (Group-Ia) or distilled water (D/W) treated group. The rise was highly significant (P<0.001). So, this result of the study indicated that adrenaline induced myocardial damage occurred.

There was a marked rise in serum AST level in the adrenaline treated group as compared to control and the rise was highly significant (P<0.001). The result is also shown in Table-III. So, these results of the part-I experiment of this study indicated that adrenaline induced myocardial damage had occurred.

Hepatic GSH contents, 12 hrs and 24 hrs after the 2nd injection of adrenaline and distilled water treatment were measured and there was a marked decrease in hepatic GSH content in adrenaline treated group as compared to control and both the changes were highly significant (P<0.001). The results were shown in Table-III.

Cardiac GSH contents, 12 hrs and 24 hrs after the 2nd injection of adrenaline and distilled water treatment were measured respectively. There were marked decrease in cardiac GSH contents in adrenaline treated group as compared to control and the reductions were highly significant (P<0.001).The results were shown in Table-III. These results of the part-I experiment of this study indicated that adrenaline caused oxidative stress on heart and liver.

In Part-II experiment, it was found that,carvedilol pretreatment decreased serum CK-MB level as compared to only adrenaline treated group of rats and the change was highly significant (P<0.001). Treatment with carvedilol prevented the adrenaline induced increase in serum CK-MB level by 79.94 % (Table-IV).

It was shown in Table-V that carvedilol pretreatment prevented the adrenaline induced rise in serum AST level by 57.35%. Carvedilol pretreatment caused attenuation in serum AST level as compared to only adrenaline treated group and the changes were highly significant (P<0.001). These results of the part-II experiment of this study indicated that carvedilol pretreatment provided effective prevention in adrenaline induced myocardial damage.

In Table-IV, it was found that an increase in hepatic GSH content (12 hrs after the 2nd injection of adrenaline) in carvedilol pretreated group as compared to only adrenaline treated group and the change was highly significant (P<0.001). Carvedilol pretreatment prevented the adrenaline induced decrease in hepatic GSH content by 80.75 % (Table-IV). Hepatic GSH contents (24 hrs after the 2nd injection of adrenaline) in carvedilol pretreated group was increased as compared to only adrenaline treated group.The increase in hepatic GSH content was highly significant (P<0.001).Carvedilol pretreatment caused 84.62% prevention in reduction of hepatic GSH content in adrenaline treated rats. The results are shown in Table-V. There was an increase in cardiac GSH contents(12 hrs after the 2nd injection of adrenaline) in carvedilol pretreated group as compared to only adrenaline treated group and the change was highly significant (P<0.001). After pretreatment with carvedilol, 59.56 % prevention of reduction of cardiac GSH content was found in adrenaline treated rats (Table-IV).

In Table-V, it was also shown that 24 hrs after the 2nd injection of adrenaline cardiac GSH content in carvedilol pretreated group was increased as compared to only adrenaline treated group and the change was significant (P<0.01). Carvedilol pretreatment prevented the adrenaline induced fall in cardiac GSH content by 74.38%. These results of the part-II experiment of this study indicated that carvedilol pretreatment provided effective antioxidative action.

Table-III: The effect of Adrenaline on serum CK-MB and AST levels and GSH contents (hepatic and cardiac) 12 hrs and 24 hrs after the 2nd injection

Variable	**Group-I(a),** (n=6) Control (D/W) (mean±SE)	**Group-II (a) ,** (n=10) 12 hrs after 2nd inj of Adrenaline (mean±SE)	**Group-I(b)**, (n=6) (mean±SE)	**Group-II (b),** (n=10) 24 hrs after 2nd inj of Adrenaline (mean±SE)
Serum CK-MB level (U/L)	9.86±1.13	48.25±1.21*		
Serum AST level (U/L)		-	192.6±4.22	428.95±4.89*
Hepatic GSH content (mg/gm of protein)	6.07±0.44	2.07±0.23*	6.10±0.63	2.20±0.13*
Cardiac GSH content (mg/gm of protein)	1.75±0.18	0.39±0.04*	1.71±0.19	0.50±0.07*

*=Highly Significant (P<0.001), n=Number of rats in the group, D/W=Distilled water. Distilled water was given 1 ml s.c. Two inj 24 hrs apart. Adrenaline was given at a dose of 2 mg/kg s.c. Two inj 24 hrs apart. Comparison was made between Group-I(a) vs Group-II (a) and Group-I(b) vs Group-II(b)

Table-IV: Effect of pretreatment of carvedilol on serum CK-MB levels and GSH contents (Hepatic and Cardiac) GSH 12 hrs after the 2nd injection of adrenaline.

Variable	**Group-I(a),** (n=6) **Control** (D/W) (mean±SE)	**Group-II (a),** (n=10) 12 hrs after 2nd inj of Adrenaline (2mg/kg) (mean±SE)	**Group-III (a),** (n =10) 12 hrs after 2nd inj of Carvedilol (1mg/kg) + Adrenaline(2mg/kg) (mean±SE)	**Prevention** by Carvedilol pretreatment
Serum CK-MB level (U/L)	9.86±1.13	48.25±1.21	17.56± 1.24 **	79.94%
Hepatic GSH content (mg/gm of protein)	6.07±0.44	2.07±0.23	5.30±0.57**	80.75%
Cardiac GSH content (mg/gm of protein)	1.75±0.18	0.39±0.04	1.20±0.13**	59.56%

**=Highly Significant (P<0.001) in respect of comparison between Group II(a) and Group-III(a), n=Number of rats in the group, D/W=Distilled water. Carvedilol was given (1 mg/kg b.w) - 1ml orally daily for 2 weeks, D/W -1ml s.c. two inj 24 hrs apart. Carvedilol (200µg) -1ml orally daily for 2 weeks followed by 1st inj of adrenaline on 15th day and 2nd inj after 24 hrs. Comparison was made between Group-II(a) vs Group-III(a)

Table-V: Effect of pretreatment of carvedilol on Serum AST level and Hepatic and Cardiac GSH content 24 hrs after the 2nd injection of adrenaline

Variable	**Group-I(b)** ,(n = 6) Control(D/W) (1.0 ml) (mean±SE)	**Group-II(b)** ,(n =10) Adrenaline (2mg/kg) (mean±SE)	**Group-III (b)**, (n =10) 12 hrs after 2nd inj Carvedilol (1mg/kg) + Adrenaline(2mg/kg) (mean±SE)	**Prevention** by Carvedilol pretreatment
Serum AST level (U/L)	192.6± 4.22	428.95±4.89	293.40±4.47**	57.35%
Hepatic GSH content (mg/gm of protein)	6.10±0.63	2.20±0.13	5.50±0.23**	84.62%
Cardiac GSH content (mg/gm of protein)	1.71±0.19	0.50±0.07	1.40±0.07**	74.38%

**=Highly Significant (P<0.001) in respect of comparison between Group II(a) and Group-III(a), n=Number of rats in the group, D/W=Distilled water. Carvedilol was given (1 mg/kg b.w) - 1ml orally daily for 2 weeks, D/W -1ml s.c. two inj 24 hrs apart. Carvedilol (200µg) -1ml orally daily for 2 weeks followed by 1st inj of adrenaline on 15th day and 2nd inj after 24 hrs. Comparison was made between Group-II(a) vs Group-III(a)

Discussion

Acute myocardial infarction (AMI) is associated with profound alteration in the sympathetic nervous system activity[29]. Sympathetic activation in AMI contributes to elevation of plasma noradrenaline levels which are associated with higher mortality in patients with IHD. Catecholamines cause cardiac myocytes dysfunction and necrosis[30].

It has been reported that during MI, the natural antioxidant defense mechanisms (i.e, superoxide dismutase, catalase and GSH) are depleted. Subsequently myocardial ischemic tissue becomes vulnerable to any type of oxidative stress which is mediated via different types of free radicals from various sources[7,31]. Since catecholamines readily undergo oxidation the oxidation products of catecholamines generate highly cytotoxic free radicals which play an important role in catecholamine induced cardio toxicity[32].

The present study was aimed to evaluate the cardio protective role of carvedilol in rat model of MI. For this purpose experimental MI was induced by injecting adrenaline sub cutaneuously on the nape of the neck of adult Long Evans rats (weighing 180-220g) at a dose of 2mg/kg body weight two injections 24hrs apart[27]. In this investigation the evidence of experimental MI was assessed by estimation of serum CK-MB and AST levels[25-28]. We also measured hepatic and cardiac GSH contents for indirect evidence of free radical induced myocardial damage in experimental MI. In this study, we measured two enzymes (serum C-MB and serum AST) as a biochemical parameter of estimation of myocardial damage experimentally after adrenaline administration.

In the present investigation, serum CK-MB level was markedly evelated 12 hrs after the 2nd infection of adrenaline. The elevation was highly significant (P< 0.001). Significantly elevated serum CK-MB level 12 hrs after the onset of experimental MI were found in some studies in BSMMU[25]. This study also showed that serum AST level was increased significantly (P<0.001) 24 hrs after the 2nd injection of adrenaline[25,27,28]. Estimation of both CK-MB and AST levels are good indicators of the extent of myocardial necrosis during AMI and increases the diagnostic accuracy of enzyme test in MI than either test alone[32].

In the present study, hepatic and cardiac GSH contents are measured for indirect evidence of free radical induced myocardial damage in experimental MI. Hepatic GSH content was significantly (P<0.001) decreased 12 hrs and 24 hrs after the adrenaline administration[11,33]. It was also observed in this study that cardiac GSH content was decreased significantly (P<0.001) in 12 hrs and 24 hrs after the onset of experimental MI. Similarly it was found in a study that a severe depletion in cardiac GSH content in MI, showing that myocardial oxidative damage had occurred[8,11]. The result of this study indicated that adrenaline administration induced myocardial damage as evidenced by increase in serum CK-MB and AST levels which were associated with free radical induced cardiac tissue damage reflected indirectly by hepatic and cardiac GSH contents depletion.

In the present investigation, it was observed that 02 weeks pretreatment with carvedilol in adrenaline treated rats caused significant (P<0.001) decrease in serum CK-MB level 12 hrs after adrenaline administration. It was also found that carvedilol pretreatment prevented the adrenaline induced rise in serum CK-MB level by 79-94%. In this study there was significant (P<0.001) decrease in serum AST level in carvedilol pretreated group and pretreatment with carvedilol prevented the adrenaline induced rise is serum AST level by 57.35%[23,25,34].

In the present study 02 weeks pretreatment with carvedilol in adrenaline treated rats caused highly significant (P<0.001) increase in hepatic GSH content 12 hrs and 24 hrs after adrenaline administration. Carvedilol pretreatment prevented the adrenaline induced decrease in hepatic GSH contents by 78.25% and 84.61% 12 hrs and 24 hrs after adrenaline administration respectively. These results are similar to those of other investigators[35,36]. In this investigation it was also showed that carvedilol pretreatment prevented adrenaline induced decrease in cardiac GSH content by 62.20% and 71.31% 12 hrs and 24 hrs after the onset of experimental MI respectively[24,37].

Finally, it was evident in this study that carvedilol in addition to its α and β blocking activity, its antioxidant activities contributed significantly to its cardiac protective effect after ischemia and reperfusion[23,24].

Conclusion

Carvedilol provided cardioprotection by blocking both β_1 and β_2 adrenoceptors. Blockade of β_1 adrenoceptor in myocardium afforded by carvedilol reduces myocardial contractility and oxygen consumption by blocking β_2-adrenoceptor prevents adrenaline stimulated noadrenaline release and subsequent auto-oxidation. Oxidation of catecholamines generate free radicals which play an important role in catecholamine induced cardioloxicity. Carvedilol also have free-radical scavenging activity which reduces oxidative stress following experimental MI.

It was concluded that carvedilol through its antioxidant property in addition to β-blocking effect prevents free radical mediated injury of catecholamine assault following onset of MI. In this study cardio protective role of carvedilol was evaluated in adrenaline induced MI. Future study is suggested to compare the cardioprotective effects of cardioselective and non-selective β-blockers.

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