

ANTIOXIDANT PROPERTY OF ANTIHYPERTENSIVE DRUGS (CARVEDILOL, ENALAPRIL, AND AMLODIPINE) ON LIVER FUNCTION IN ANIMAL (RATS) MODELS

PUSULOORI RAJESH*

Department of Pharmacology, Kurnool Medical College, Kurnool, Andhra Pradesh, India. Email: drpusuloorirajesh@yahoo.co.in

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ABSTRACT

Objective: The antihypertensive drugs (beta-blockers - carvedilol, calcium channel blocker - amlodipine, and angiotensin-converting enzyme inhibitor - enalapril) were investigated for its hepatoprotective effect by antioxidant property against carbon tetrachloride (CCl₄)-induced acute liver damage on albino rats.

Methods: In this study the liver was damaged by giving Carbon tetra chloride (CCl₄)-1 ml/kg-p.o. After giving CCl₄ (1 ml/kg), it significantly elevated the serum levels of biochemical markers such as serum glutamate-pyruvate transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, protein, and depleted antioxidant enzymes glutathione. After treatment with carvedilol (10 mg/kg), enalapril (0.5 mg/kg), and amlodipine (10 mg/kg) for 2 weeks, these drugs were significantly reduces the elevated levels of biochemical markers mentioned above.

Conclusion: These results suggest that these antihypertensive drugs may have the potential therapeutic value in the treatment of CCl₄-induced hepatic damage and some liver diseases. Hepatoprotective activity of these drugs may be attributed to the antioxidant principles in it.

Keywords: Antioxidant, Carvedilol, Enalapril, Amlodipine, Carbon tetrachloride, Hepatoprotective.

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INTRODUCTION

In the treatment of hypertension, many drugs such as beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are commonly used. Sometimes, combination of these drugs more effective than individual drugs [1]. These drugs also contain antioxidant compounds which protect the cells against the damaging effects of reactive oxygen species (ROS). ROS such as superoxide anion, hydroxyl radical, and hydrogen peroxide play a crucial role in the development of various ailments such as arthritis, asthma, dementia, mongolism, carcinoma, and Parkinson's disease [2]. The free radicals in the human body are generated through aerobic respiration or from exogenous sources [3]. Some of the *in vivo* free radicals play a positive role in phagocytosis, energy production, and regulation of cell growth. However, free radicals may also be damaging. Free radicals produced in the body react with various biological molecules namely lipids, proteins, and deoxyribonucleic acids resulting in the imbalance between oxidants and antioxidants. Even though our body is safeguarded by natural antioxidant defense, there is always a demand for antioxidants from secondary sources. According to literature available, these antihypertensives are also having antioxidant property [4,5]. In the present study, the antihypertensives were selected to evaluate its antioxidant potential on laboratory animal model.

METHODS

Before conducting this study, the Institutional Animal Ethical Committee permission was taken. This study was conducted strictly according to the CPCSEA guidelines.

Experimental design

The animals used for the experiment were divided into five groups and six rats for each group. Food was withdrawn 12 hr before carbon tetrachloride (CCl₄) administration to enhance the acute liver toxicity in all test groups of animal models [6].

Grouping of rats

Group: I (control): Treated with 2% gum acacia - 2 ml/100 g
Group: II (standard): Treated with silymarin (100 mg/kg)

Group: III (T-1): Treated with carvedilol (10 mg/kg/day, orally)

Group: IV (T-2): Treated with enalapril (0.5 mg/kg/day, orally)

Group: V (T-3): Treated with amlodipine (10 mg/kg/day, orally).

All the groups were treated with test drugs orally 1 hr before CCl₄ administration. After 1 hr of giving test drugs to all groups of animal, hepatic injury was induced by intraperitoneal injection of 1:1 v/v CCl₄ in olive oil (1 ml/kg) daily for 14 days. On the 15th day, all the animals were anesthetized, and blood was collected from the carotid artery at the neck for the determination of enzyme levels in serum, and then, all animals were sacrificed [7].

RESULTS

All the groups (I-V) of animals were treated with three test drugs - carvedilol (10 mg/kg), enalapril (0.5 mg/kg), and amlodipine (10 mg/kg) for test groups, 2% gum acacia - 2 ml/100 g for control group and silymarin (100 mg/kg) for standard group, 1 hr before giving CCl₄ (1 ml/kg). The carvedilol- and silymarin-treated animals were shown a significant reduction in serum marker enzymes (p<0.001). Carvedilol (10 mg/kg) and silymarin (100 mg/kg) greatly reduce enzyme levels, but enalapril (0.5 mg/kg) and amlodipine (10 mg/kg) have shown less effect than carvedilol and silymarin but have shown better effect than CCl₄-induced hepatotoxicity in control group rats [8]. Liver weight almost comes to normal.

Statistical analysis

The results obtained were expressed as mean±standard error of the mean and were analyzed by the application of one-way analysis of variance, and p<0.05 was considered significant.

All the results were depicted in Table 1.

Histological examination of the hepatic tissue in CCl₄-treated rats shown that CCl₄ had produced profound inflammation and congestion particularly in sinusoids. Pre-treatment of animals with silymarin (100 mg/kg) in Group-II and carvedilol, Enalapril, and amlodipine in Group-III, IV, V respectively have not shown any pathological change in histological study.

Table 1: Effect of antihypertensive drugs on liver function (n=6, Mean±SEM)

Groups (I-V)	SGOT (IU/ml)	SGPT (IU/ml)	ALP (IU/ml)	Total bilirubin (Mg/dl)	Liver weight (g/100 g bw)
Control (CCl ₄ -1 ml/kg)	259.8±0.60	255.63±1.21	222.2±0.36	2.05±0.03	3.71±0.03
Standard (silymarin-100 mg/kg)	161.2±0.21***	149.35±0.15***	169.4±0.31***	0.79±0.05***	2.56±0.01***
Test-1 (carvedilol-10 mg/kg)	177.7±0.10**	182.45±1.15**	173.8±0.13**	1.11±2.21***	3.10±0.01**
Test-2 (enalapril-0.5 mg/kg)	192.4±0.09*	200.65±2.33*	211.5±0.14*	1.86±0.03**	3.73±0.50*
Test-3 (amlodipine-10 mg/kg)	201.2±0.22*	223.42±5.31*	201.9±0.17	2.20±3.31*	3.51±0.02*

*p<0.05, **p<0.01, ***p<0.001 compared to control. SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate-pyruvate transaminase, ALP: Alkaline phosphatase, CCl₄: Carbon tetrachloride

DISCUSSION

In the present study, these antihypertensive drugs (carvedilol, enalapril, and amlodipine) were selected to prove its antioxidant effect by hepatoprotective activity scientifically using experimental animal models. Selection of these drugs for this study is due to its cardioprotective activity, vascular protective activity by reducing vascular stress in the treatment of hypertension. Stress-reducing property of these drugs may be due to antioxidant activity on the blood vessels, renal system, and cardiac muscle [9]. CCl₄-induced hepatic damage in rats model was used for the study. CCl₄ is commonly used drug to induce hepatotoxicity by generating free radicals in the experimental study [10]. Liver damage was confirmed by high serum enzymes (serum glutamic oxaloacetic transaminase, serum glutamate-pyruvate transaminase, alkaline phosphatase, and tuberculosis) levels because they are cytoplasmic in location and released into circulation after hepatocyte damage. Liver weight also increased due to toxic effect of CCl₄. Due to antioxidant property of these antihypertensive drugs inhibit the generation of free radicals in hepatotoxicity induced by CCl₄ in rats

The carvedilol- and silymarin-treated animals were shown a significant reduction in serum marker enzymes (p<0.001). Carvedilol (10 mg/kg) and silymarin (100 mg/kg) greatly reduce enzyme levels, but enalapril (0.5 mg/kg) and amlodipine (10 mg/kg) have shown less effect than carvedilol and silymarin but have shown better effect than CCl₄-induced hepatotoxicity in the control group rats. Liver weight almost comes to normal [11,12].

Its probable mechanism in hepatic damage was antioxidant effect by preventing free radical releasing. In histological examination also, no inflammatory cells and very less necrotic cells were appeared with carvedilol (Group-III) treated (10 mg/kg) and silymarin (Group-II)-treated groups. Few inflammatory cells were appeared in enalapril-treated (0.5 mg/kg) and amlodipine-treated groups (10 mg/kg). Serum enzymes levels were also comes to normal. The weight of the liver also in both the models was effectively reduced in carvedilol- and silymarin-treated groups when compared with the control group.

CONCLUSION

The present study indicates that the antihypertensive drugs (carvedilol, enalapril, and amlodipine) have potential hepatoprotective activity by

its antioxidant property. Hence, these drugs can be used as antioxidants in various conditions. However, it needs further clinical trials before complete trust and usage.

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