Effects of Carvedilol on the antioxidant mechanisms of blood cells in IHD patients treated with isosorbide dinitrite

Article · January 2000

CITATIONS
0

READS
7

2 authors:

Saad Hussain
Alrafidain University College, Baghdad, Iraq
171 PUBLICATIONS **530** CITATIONS
SEE PROFILE

Nawfal A. Numan
Baghdad Pharmacy College
20 PUBLICATIONS **23** CITATIONS
SEE PROFILE

...l. Sci. 2000 : 3(4) , 41-50 .

...ts of Carvedilol on The Antioxidant Mechanisms of Blood ...ells In IHD Patients Treated With Isosorbide Dinitrate

Saad A. Hussain * , Nawfal A. Numan **

الملخص:

تم قياس محتوى الخلايا الحمراء والبيضاء من مادة الكلوتاثيون (GSH) والمالوناي الديهايد (MDA) المترابطة بالاضافة الى فعالية الانزيمات المضادة لتاكسد (GSH-Px, GST, GSR) الكاتليز و (SOD) في إقفار العضلة القلبية المعالجين بـ 20 ملغم في اليوم من مادة الآيزوسورباید ثنائي النترات لوحده ومع ولحد بيتا، البروبرانولول او الكافيديلول. وتبين من الدراسة ان الاصابة باقفار القلب والعلاج بالآيزوسورباید ثنا لوحده يؤدي الى استنفاذ الكلوتاثيون، وزيادة أدلة تاكسد الشحوم مثل MDA والدبينات وتحفيز شديد المضادة للتاكسد في خلايا الدم الحمراء والبيضاء.

إن اضافة 25 ملغم في اليوم من عقار الكارفيديلول مثبط بيتا الذي يحتوي على خواص مضادة للت الايزوسورباید ثنائي النترات يؤدي الى تحسين حالة فرط الاكسدة التي سببها الايزوسورباید واقفار العضل والمتمثل بارتفاع مستوى GSH وقلة مستوى MDA والدبينات نتيجة لتقليل اكسدة الشحوم بالاضافة الى ت فعالية الانزيمات المضادة للتاكسد.

ولم يثبت من خلال الدراسة ان البروبرانولول، العلاج ، العلاج الروتيني المستخدم في هذه الحالة له مثل هذ الآنفة الذكر التي احدثها الكارفيديلول مما يدعم خاصيته المضادة للتاكسد وضرورة استخدامه في مثل هذه الحا

...ct

...ocytes and leukocytes reduced glutathione (GSH) malondialdehyde (MDA) and conju...es, and the activities of glutathione-s-transferase (GST), glutathione peroxidase (GSH-...thione reductase (GSR), catalase and superoxide dismutase (SOD) have been investi... ischemic heart diseases (IHD) patients treated with 20 mg/day isosorbide dinitrate ...one, and with one of the (-blockers, propranolol or carvedilol.

...ocytes and leukocytes GSH was found to be severely depleted with significant elevation ...d conjugated dienes, the parameters of lipid peroxidation, and the activities of GST, ...GSR, catalase and SOD were induced as a results of IHD attack and ISDN treatment ...pared to normal controls.

...istration of 25 mg/day carvedilol, a (-blocker with antioxidant properties with ISDN ...ignificant improvement in the oxidative stress state in blood cells of IHD patients pro... ISDN, reflected by increasing GSH levels, decreasing MDA and conjugated dienes lev... decreasing the activities of the antioxidant enzymes.

...anolol, the routinely used (-blocker, has no such effect.

...tment of Community Health, Baquba Institute of Technology, Diyala, Iraq.
...rtment of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, ...dad, Iraq.

Key words :*Carvidelol, Antioxidant enzymes, Lipid peroxidation, Ischemic heart diseases.*

Introduction

Carvedilol is a vasodilating, beta-adrenoceptor antagonist currently marketed for the treatment of mild to moderate hypertension [1]. It reduces total peripheral resistance by blocking peripheral vascular alpha 1- adrenoceptors, thereby producing systemic arterial vasodilitation, while inhibiting reflex tachycardia through the blockade of myocardial beta-adrenoceptors [2]. Carvedilol, as well as some of its hydroxylated metabolites, are potent antioxidants, in physicochemical, biochemical and cellular assays, they prevent lipid peroxidation and the depletion of endogenous antioxidants, such as vitamin E and glutathione [3]. It was found to protect rat aorta rings from free radical-induced endothelial cell dysfunction, which is not seen with propranolol, a pure beta-receptor antagonist [4].

In experimental models, carvedilol was shown to protect LDL from in vitro oxidation, and to prevent oxidized LDL-induced leukocytes adhesion to smooth muscle cells and oxidized LDL-promoted cytotoxicity [5,6].

New evidences indicated that severe disturbances in the antioxidant profile of blood cells were observed in patients with unstable angina and acute myocardial infarction [7], and plasma malondialdehyde (MDA) was found to be deeply affected in patients suffering from acute myocardial infarction, indicating the occurrence of oxygen radicals-mediated injury in humans [8]. The exogenous compensatory supply of organic nitrates as a source of nitric oxide in ischemic heart diseases patients, was found to worsen the case of oxidative stress and produces further impairment in the antioxidant profile of blood cells [9].

The use of synthetic compounds with inherited antioxidant properties in this respect, was recently considered an attractive approach in this field [10,11].

This study was designed to evaluate the effects of carvedilol on the oxidative stress and antioxidant profile in blood cells of ischemic heart diseases patients who are maintained on chronic treatment with a fixed dose of isosorbide dinitrate.

Patients and Methods

A. Patients Selection and Drug Treatment:

20 patients with IHD (angina pectoris and myocardial infarction), who are maintained on 20 mg/day isosorbide dinitrate orally, were selected. 10 of them received 25 mg/day carvedilol (Bohringer Manhiem, Germany) for 90 days, and the other 10 received 40 mg/day pro-

ol (ICI company, England) for comparison. 8 patients with acute IHD attack, were se- to evaluate the studied parameters before any treatment intervention.

l values for the studied parameters were obtained from 24 healthy subjects, with s matched with those of IHD patients to exclude the effects of age variations.

d samples were collected from normal subjects, and from IHD patients after 90 days ment by veinpuncture in pre-cooled, EDTA-containing tubes and stored at 4°C unless d immediately.

Analytical Methods:

hrocytes were separated and hemolysate was prepared according to the method of dy, 1971 [12]. Leukocytes fraction of the blood was separated utilizing the modified d of Salin and McCord, 1974 [13]. Erythrocytes and leukocytes reduced glutathione) content was determined according to the method of Ellman, 1959 [14]. Lipid peroxi- parameters were evaluated by measurement of malondialdehyde (MDA) using the thi- turic acid method of Beuge and Aust, 1978 [15], while erythrocytes and leukocytes ated dienes levels were assayed according to the method of Recknagel and Goshal, 6].

rocytes and leukocytes glutathione-s-transferase enzyme (GST) activity was estimat- ding to the method of Habig et al., 1974 [17]. Glutathione reductase (GSR) activity sured according to the method of Beultler, 1969 [18]. Selenium-dependent glutathi- oxidase (GSH-Px) activity was determined by the coupled-assay procedure of Paglia ntine, 1967 [19], as modified by Lee et al., 1981 [20].

e enzyme activity was assayed by the method of Aebi, 1974 [21], and Zn-Cu- dismutase (SOD) activity was measured by the method of Wenterboum et al., Total cytosolic protein determination was performed by the standard method of et al., 1951 [23].

tatistical evaluation of data was performed through two-ways comparison of data utiliz- Student's t-test.

esults

A. Blood Cells Glutathione (GSH) Levels:

The effects of the two (-blockers, propranolol and carvedilol, on the isosorbide dinitrate SDN)-induced depletion of erythrocytes and leukocytes glutathione levels are shown in ta- le 1. 40 mg/day propranolol shows no significant changes in glutathione levels when given

with 20 mg/day ISDN, compared to ISDN alone, which produces significant depletion of GSH in erythrocytes and leukocytes compared to normal controls and IHD patients before any treatment. 25 mg/day carvedilol produced 300% and 280% increase in erythrocytes and leukocytes GSH content respectively, compared to ISDN treatment only. This elevation in GSH levels in both compartments was significantly higher than that in IHD patients before starting any treatment, but still not enough to match normal control levels.

B. Lipid Peroxidation:

Carvedilol was found to produce significant reduction in MDA production, 70% and 60% in both compartments respectively, compared to propranolol, which did not produce any significant change in MDA levels previously elevated by IHD attack and treatment with 20 mg/day ISDN, compared to normal controls (table 2). Conjugated dienes, the other parameter of lipid peroxidation, was found to be elevated significantly during IHD attack, and treatment with 20 mg/day ISDN worsens the case. Addition of 40 mg/day propranolol did not change conjugated dienes levels in both compartments (table 2). Carvedilol 25 mg/day produced significant reduction in erythrocytes and leukocytes conjugated dienes levels, (73% and 80% respectively) compared to propranolol treatment.

C. Glutathione Metabolizing Enzymes Activities:

Glutathione-S-transferase activity, which is greatly induced during IHD attack and after treatment with 20 mg/day ISDN, show 21% increase in activity in both compartments after 40 mg/day propranolol compared to ISDN treatment alone (table 3). Carvedilol produced no changes in GST activity compared to propranolol treatment.

Table 4 indicates that addition of 40 mg/day propranolol to 20 mg/day ISDN produced no significant changes in glutathione peroxidase (GSHñiPx) activity in both compartments, which was highly induced by the use of 20 mg/day ISDN alone.

Carvedilol 25 mg/day caused 60% and 55% decrease in (GSH-Px) activity in both compartments, respectively, which is considered highly significant ($P<0.01$) compared to propranolol treatment.

Glutathione reductase (GSR) activity was greatly induced in both erythrocytes and leukocytes when IHD patients were treated with 20 mg/day ISDN. 40 mg/day propranolol produced no significant changes in GSR activity. When carvedilol 25 mg/day was used, it produced a highly significant decrease, (40% and 55%) respectively, in erythrocytes and leukocytes GSR activity (table 4) compared to propranolol treatment.

...depletion of ...tients before ...rocytes and ...elevation in ...ients before

...% and 60% ...ce any sig- ...ith 20 mg/ ...rameter of ...treatment ...ot change ...duced sig- ...d 80% re-

...and after ...nts after ...duced no

...duced no ...rtments,

...th com- ...to pro-

...leuko- ...ol pro- ...it pro- ...es and

...lase and Superoxide Dismutose (SOD) Enzymes Activities:

...e 5, carvedilol treatment (25 mg/ day) with 20 mg/day ISDN produced significant ...erythrocytes and leukocytes catalase activity, 55% and 50% respectively, com- ...previously elevated activity produced by IHD attack and ISDN treatment alone.

...dismutase (SOD) activity decreased significantly when carvedilol 25 ...ed in IHD patients treated with 20 mg/day ISDN table 5. SOD activity in ...leukocytes of IHD patients decreases by 40% and 58% respectively due to ...ent, compared to propranolol treated group.

...on of (-adrenoceptors blocking agents and vasodilators have been widely used ...of IHD, because of their favorable hemodynamic actions, and their high effica-

...e enhanced production of free radicals due to ischemic changes, and use of vari- ...s of ISDN impairs the antioxidant defense system of the blood cells, with conse- ...crease in lipid peroxidation in IHD patients [9], an adequate antioxidant supply ...e included in the therapeutic measures. This can be achieved either with concomitant ...entation of antioxidants with the combined vasodilator and (-blocker therapy, or al- ...ely, with the administration of single drug exhibiting intrinsic antioxidant properties ...tion to the specific vasodilator effect, like Nicorandil [24], or specific (-blocker agent ...ing intrinsic antioxidant properties like carvedilol.

...rvedilol has been shown to produce significant cardioprotection in experimental animal ...ls of acute myocardial infarction. It also prevents lipid peroxidation and the depletion of ...enous anti oxidants such as vitamin E and glutathione [25].

...e data indicated the improving effects of treatment with 25 mg/day of carvedilol on the ...peroxidation and antioxidant system in blood cells of IHD patients who are previously ...ained on 20 mg/day ISDN. These observed effects are completely compatible with ...e observed by Maggi et al. (1996), who indicated that a correct pharmacological ap- ...ch to the treatment of patients with essential hypertension should be focused not only on ...cing blood pressure, but also on preventing lipid preoxidation with agents like carvedilol ...]. The results of this study indicated that the effects of carvedilol was attributed to its in- ...ited antioxidant properties and not to the other hemodynamic changing properties, this ...s explained carefully when compared with the data of patients treated with 40 mg/day pro- ...ranolol, the other (-adrenoceptor blocking agent.

The antioxidant properties of carvedilol have been investigated extensively in a variety of

in vitro models including isolated lipoproteins [5], subcellular fractions [27], cell cultures [6] and in some other more complex animal models [28]. The potent antioxidant properties of carvedilol are found to prevent lipid peroxidation of mitochondrial membranes with consequent contribution to the known cardioprotective activity in ischemic heart diseases [29].

Accumulating experimental evidences indicated that oxygen free radicals are overproduced during IHD and ISDN treatment, and this may include superoxide anion, peroxynitrite generated during reaction of nitric oxide radical with superoxide anion itself [30], and the extremely reactive hydroxyl radical. Therefore, we can conclude that, carvedilol exert its effects, by scavenging these oxidant species, leading to the observed improvement shown in our study.

References

1. Strein, K. and Sponer, G.(1990) Experimental and Clinical pharmacology of carvedilol and other drugs containing vosodilitation and beta-adrenoceptor antagonism in a single molecule. *Zeitshrift fur Kardiologie* **29(3)**, 89.
2. Morito, K., Hamano, S., Yoshizumi, M. and Oka, M.(1989) Inhibitory action of carvedilol on catecholamine secretion and calcium influx in cultured bovine adrenal chromaffin cells. *Biochemical Pharmacology* **38(24)**, 4461.
3. Feuerstein, G. Z. and Ruffolo, R. R.(1995) Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection. *Eur. Heart J.* **16(1)**, 38.
4. Lopez, B. L., Christopher, T. A., Yue, T. L., Ruffolo, R., Feuerstein, G. Z. and Max, X. L. Carvedilol, (1995) a new beta-adrenoceptor blocker antihypertensive drug, protects against free radical induced endothelial dysfunction. *Pharmacology*. **51(3)**, 165.
5. Yue, T. L., McKenna, P. J., Lysko, P. G., Ruffolo, R. R. and Feuerstein, G. Z.(1992) Carvedilol, a new antihypertensive, prevents oxidation of human low density lipoproteins by macrophage and copper. *Atheroseclerosis*, **97**, 209.
6. Yue, T. L., Wang, X., Gu, J. L., Ruffolo, R. R. and Feuerstein, G. Z. (1995) Carvedilol, a new vasodilating beta-adrenoceptor blocker inhibits oxidation of low density lipoprotiens by vascular smooth muscle cells and prevents leukocytes adhesion to smooth muscle cells. *J. Pharmacol. Exp. Ther.* **273**; 1442(1995).
7. Dubious-Rande, J. L., Artigou, J. Y., Darmon, J. Y., Habbal, R., Manuel, C., Tayarani, I. Costaigne, A. and Grosgogeat, Y. (1994)Oxidative stress in patients with unstable angina. *Eur. Heart J.* **15**, 197.

...n, G., Tavazzi, B., Di-Pierro, D., Vagnozzi, R., Penco, M. and Gairdina, B. ...e relvence of malondialdehyde as a biochemical marker of lipid peroxidation. ...ce Elem. Res. 47, 165.

...S. A., Numan, N. A. and Woheid, S. A.(1999) Dose dependent effects of iso-...rate on the antioxidant profile of blood cells of IHD patients. *Iraqi J.* ... In Press .

...V. V. and Dickstein, K.(1996) Novel drugs and current therapeutic ap-...e treatment of heart failure. *Drugs* **51(3)**, 347.

...C., Nelson, A. H., Ohlestein, E. H., Willette, R. N., Sealey, J. E., Laragh, J. ...ll, W. G. and Feuerstein, G. Z.(1996) Chronic carvedilol reduces mortality ...damage in hypertensive strock-prone rats, *J. Pharmcol. Exp. Ther.* **279**, 948.

...dy, T. L. The auto-oxidation of red cells. *Br. J. Hematol.* **20**, 457.

..., M. L. and McCord, J. M. (1947) Superoxide dismutase in polymorphonuclear ...cytes. *J. Lab. Invest.* **54**, 1005.

...man, G. I.(1959) Tissue sulfhydryl group. *Arch. Biochem. Biophys.* **82**,70.

...Buege, J. A. and Aust, S. D(1978). Microsomal lipid peroxidation. *Meth. Enzymol.* ..., 302.

... Recknagel, R. O. and Goshal, A. K.(1966) Conjugated dienes are products of microso-...mal lipid peroxidation. *Exp. Mol. Pathol.* **5**, 413.

... Habig, W. H., Pabst, M. J. and Jakoby, W. B.(1974) Glutathione-s-transferase: The ...first enzymatic step in mercapturic acid formation. *J. Biol. Chem.* **249**, 7130.

... Beutler, E.(1969). In: Functions of Glutathione. (Nabel Conf.) P-65, New York, Raven ...Press.

... Paglia, D. E. and Valentine W. N.(1967) Studies on the quantitative characterization ...of erythrocyte glutathione peroxidase. *J. Lab. Clin. Med.* **70,** 158.

... Lee, Y. H., Layman, K. K. and Bell, R. R(1981). Glutathione Peroxidase activity in ...iron deficient rats. *J. Nutr.* **111**, 194.

21. Aebi, H. Catalse. (1974) In: Methods in Enzymatic Analysis. Bergmeyer, H. V. (ed.), Verlag Chemie, Weinheim, P-673, .

22. Winterbourn, C. C., Hawkins, R. E., Brian, M. and Carrel, R. W.(1975) The estimation of red cell superoxide dismutase activity. *J. Lab. Clin. Med.* **85**, 337.

23. Lowry, D. H., Rosebrough, N. J., Farr, A. L. and Randal, R. J(1951). Protein measurement with the folin-phenol reagent. *J. Biol. Chem.* **193**, 265.

24. Naito, A., Aniya, Y. and Sakanashi, M.(1994) Antioxidant action of the nitrovasodilator nicorandil, inhibition of oxidative oxidation of liver microsomal glutathione-s-transferase and lipid peroxidation. *Jpn. J. Pharmacol.* **65**, 209.

25. Bohm, M. and Erdman, E.(1996) Therapy with beta-blockers in heart failure, recent studies with carvedilol. *Fortschr. Med.* **114(13)**, 167.

26. Maggi, E., Marchesi, E., Covini, D., Negro, C., Perani, G. and Bellomo, G.(1996) Protective effects of carvedilol, a vasodilating, (-adrenoceptor blocker, against in vivo LDL oxidation in essential hypertension. *J. Cardiovase. Pharmacol.* **27**, 532.

27. Yue, T. L., Cheng, H. Y. and Lysko, P. G.(1992) Carvedilol, a new vasodilator and beta-adrenoceptor antagonist, is an antioxidant and free radical scavenger. *J. Pharmacol. Exp. Ther.* **263**, 92.

28. Lysko, P. G., Webb, C. L. and Feuerstein, G. Z.(1994) Neuroprotective effects of carvedilol, a new antihypertensive as a Na+ channel modulator and glutamete transport inhibitor. *Neurosci. Lett.* **171**, 77.

29. Moreno, A. J., Santos, D. J. and Palmeira, C. M(1998). Ischemic heart disease: Carvedilol prevents lipid peroxidation of mitochondrial membranes. *Rev. Port. Cardiol.* **17(2)**, 1163.

30. Beckman, J. S., Chen, J., Ischiropoulos, H. and Crow, J. P.(1994) Oxidative chemistry of peroxynitrite. *Methods in Enzymol.* **233**, 229.

Table (1): Effects of (-blockers, Propranolol and Carvedilol, on Erythrocytes and Leukocytes Glutathione Levels of Ihd Patients Maintained on 20 Mg/day Isosorbide Dinitrate.

Treatment of Patients Groups	n	Glutathione µmole/ mg Protein	
		Erythrocyte	Leukocyte
Control	24	7.5 ± 0.9^a	4.2 ± 0.5^a
Acute IHD Before Treatment	8	3.0 ± 0.2^b	2.1 ± 0.1^b
ISDN 20 mg/day	20	1.2 ± 0.05^c	0.8 ± 0.02^c
ISDN 20 mg/day + PR 40 mg/day	10	1.15 ± 0.14^c	0.85 ± 0.03^c
ISDN 20 mg/day + CA 25 mg/day	10	4.6 ± 0.32^d	3.3 ± 0.12^d

- n = Number of subjects.
- Values with non-identical superscripts (a, b, c, d) are significantly different ($P < 0.05$)
- (ISDN) Isosorbide dinitrate , (PR) Propranolol, CA Carvedilol.

...sodila-
...ione-s-
recent
...6) Pro-
...n vivo
...or and
...arma-
...f car-
...ort in-
Car-
...rdiol.
...istry
...ytes
...rate.

...2): Effects of (-blockers, Propranolol and Carvedilol, on The Lipid Peroxidation Parameters, Mda And Conjugated Dienes Levels in Erythrocytes and Leukocytes of Ihd Patients Maintained on 20 Mg/day Isosorbide Dinitrate.

...tment of ...ts Groups	n	MDA Nmole/mg Protein		Conjugated Dienes µmole/ l	
		Erythrocyte	Leukocyte	Erythrocyte	Leukocyte
...ontrol	24	0.31 ± 0.05^a	0.52 ± 0.1^a	0.5 ± 0.01^a	0.81 ± 0.1^a
...te IHD	8	2.5 ± 0.3^b	3.75 ± 0.21^b	3.8 ± 0.35^b	5.0 ± 0.8^b
...Treatment					
...20 mg/day	20	4.73 ± 0.72^c	5.02 ± 0.16^c	6.2 ± 1.1^c	12.3 ± 1.5^c
...20 mg/day + ...40 mg/day	10	4.85 ± 0.72^c	5.1 ± 0.81^c	6.7 ± 2.0^c	11.5 ± 3.0^c
...N 20 mg/day + ...A 25 mg/day	10	1.43 ± 0.19^d	2.05 ± 0.1^d	1.8 ± 0.3^d	3.3 ± 0.12^d

...Number of subjects.
...es with non-identical superscripts (a, b, c, d) are significantly different ($P < 0.05$)
...DN) Malondialdehyde, (ISDN) Isosorbide dinitrate, (PR) Propranolol, CA Carvedilol.

...le (3): Effects of (-blockers, Propranolol And Carvedilol, on Erythrocytes and Leukocytes Glutathione-s-transferase (Gst) Activity in Ihd Patients Maintained on 20 Mg/day Isosorbide Dinitrate.

Treatment of Patients Groups	n	GST Activity u/mg Protein	
		Erythrocyte	Leukocyte
Control	24	0.41 ± 0.05^a	10.2 ± 1.3^a
Acute IHD	8	6.82 ± 1.1^b	18.3 ± 2.4^b
...efore Treatment			
...SDN 20 mg/day	20	19.6 ± 2.5^c	41.15 ± 4.7^c
ISDN 20 mg/day + PR 40 mg/day	10	23.8 ± 3.6^d	50 ± 4.9^d
ISDN 20 mg/day + CA 25 mg/day	10	21.2 ± 3.0^d	47 ± 5.0^d

- n = Number of subjects.
- Values with non-identical superscripts (a, b, c, d) are significantly different ($P < 0.05$)
- (ISDN) Isosorbide dinitrate, (PR) Propranolol, CA Carvedilol.

Table (4): Effects of ß-blockers, Propranolol and Carvedilol, on Erythrocytes and Leukocytes Gsh-px and Gsr Enzymes Activities in Ihd Patients Maintained on 20 Mg/day Isosorbide Dinitrate.

Treatment of Patients Groups	n	GSH-Px Activity u/mg Protein		GSR Activity u/mg Protein	
		Erythrocyte	Leukocyte	Erythrocyte	Leukocyte
Control	24	2.8 ± 0.04^a	3.1 ± 0.15^a	0.68 ± 0.01^a	5.58 ± 1.1^a
Acute IHD Before Treatment	8	3.0 ± 0.36^a	5.8 ± 0.6^b	1.4 ± 0.4^b	7.26 ± 1.5^b
ISDN 20 mg/day	20	12.3 ± 2.6^b	14.5 ± 3.0^c	9.8 ± 2.1^c	24.8 ± 3.9^c
ISDN 20 mg/day + PR 40 mg/day	10	12.75 ± 3.0^b	13.8 ± 1.9^c	11.6 ± 1.9^c	24.0 ± 4.2^c
ISDN 20 mg/day + CA 25 mg/day	10	5.2 ± 0.9^c	6.1 ± 1.1^b	6.9 ± 1.2^b	10.8 ± 1.8^d

- n = Number of subjects.
- Values with non-identical superscripts (a, b, c, d) are significantly different ($P < 0.05$).
- (ISDN) Isosorbide dinitrate, (PR) Propranolol , (CA) Carvedilol, (GSH-Px) Glutathione peroxidase, (GSR) Glutathione reductase.

Table (5): Effects of ß-blockers, Propranolol and Carvedilol, on Erythrocytes and Leukocytes Catalase and Superoxide Dismutase (Sod) Enzymes Activities in Ihd Patients Maintained on 20 Mg/day Isosorbide Dinitrate.

Treatment of Patients Groups	n	Catalase Activity u/mg Protein $x10^3$		Superoxide Dismutese Activity u/mg Protein $x\ 10^2$	
		Erythrocyte	Leukocyte	Erythrocyte	Leukocyte
Control	24	1.3 ± 0.08^a	0.15 ± 0.01^a	4.21 ± 0.6^a	7.6 ± 1.2^a
Acute IHD Before Treatment	8	2.16 ± 0.31^b	2.3 ± 0.3^b	6.8 ± 0.7^b	18.3 ± 3.0^b
ISDN 20 mg/day	20	5.6 ± 0.9^c	11.3 ± 1.2^c	12.5 ± 2.1^c	28.9 ± 2.6^c
ISDN 20 mg/day + PR 40 mg/day	10	6.1 ± 1.5^c	11.8 ± 0.95^c	11.8 ± 2.6^c	27.0 ± 4.0^c
ISDN 20 mg/day + CA 25 mg/day	10	2.8 ± 0.26^d	5.9 ± 0.51^d	7.1 ± 1.0^d	11.3 ± 1.7^d

- n = Number of subjects.
- Values with non-identical superscripts (a, b, c, d) are significantly different ($P < 0.05$).
- (ISDN) Isosorbide dinitrate, (PR) Propranolol , (CA) Carvedilol.

Accepted : 23/08/2000 - Received: 08/03/2000