International Journal of Medicine Research
ISSN: 2455-7404; Impact Factor: RJIF 5.42
www.medicinesjournal.com
Volume 1; Issue 2; May 2016; Page No. 148-151

Effects of bisoprolol and nebivolol on the spectrum of essential amino acids in the blood serum of patients with unstable angina

[1] Zavalskaya TV, [2] Dr. Lizogub VG

[1] Department of General Medicine №4, Bogomolets National Medical University, Ukraine
[2] Professor, Head of the Department, Bogomolets National Medical University, Ukraine

Abstract
The study involved patients with unstable angina. Ion exchange liquid-column chromatography method was used. Levels of non-essential amino acids was determined in the blood plasma. In patients with unstable angina, antianginal therapy which include Nebivolol, compared with patients taking bisoprolol, serum normalized level of ornithine, taurine, tyrosine. In both groups returned to normal levels of glutamine.

Keywords: Unstable angina, amino acid, antianginal therapy, bisoprolol, nebivolol.

1. Introduction

One of the most important mediators that are functionally involved in different biological processes, is nitric oxide (NO). NO indirectly causes relaxation of the muscular layer. One of the most important and most studied target organ for NO is the cardiovascular system, where it becomes one of the regulatory factors, carrying out in particular cardio protective functions, enhances the body's needs in the local perfusion in ischemic conditions (Bulanova E.L. *et al*, 2014; Ivashkin V.T. *et al*, 2001) [1, 3]. NO is synthesized in the coronary endothelium, endocardium, cardiomyocytes. Increased levels of NO in intracellular concentration of cGMP, increases ventricular diastolic relaxation and tension, improving the contractile function of the myocardium. Under experimental conditions, it was found that NO has a marked influence on the heart and hemodynamics, causing a decrease in heart rate, stroke volume, increased PQ interval duration and blood expulsion period. Probably, NO, resulting in cardiomyocytes provides b-adrenergic negative inotropic and chronotropic action (Nasyrova A.G., 2004; Brutsaert D.L., 2003) [9, 12]. As NO is synthesized in the vascular endothelium, it is involved in the regulation of the tone as an antagonist of the adrenergic nervous system.

Given these effects of NO, drugs of interest, which are its donators or potentiate its release by the endothelium. Drug of choice, in particular, β-blockers (BAB), nebivolol (nebilet, binelol) Nebivolol (Nebilet, Berlin-Chemie) - a highly selective blocker of β 1-adrenergic receptors 3rd generation. A feature of this product is its ability to stimulate the synthesis of NO by the endothelium due to the effect of beta-adrenergic receptors are 3 types. Probably, their stimulation causes the release of NO by the endothelium. In atrial tissue this receptor subtype is involved in the regulation of ion channels. The functions of these receptors in adipose tissue lipolysis and include regulation of carbohydrate metabolism (Moshkovska Yu. O., 2015) [8].

Since 2005, nebivolol is included in the European guidelines for the treatment of cardiac insufficiency, regardless of gender, age and ejection fraction of the left ventricle (Kovalenko V.M. *et al*., 2007) [5].

The ability to influence on lipid metabolism, increase blood glucose and blood lipid levels gave reasons to the Recommendations of the European Society of Cardiology in 2007 to limit the use of beta-blockers, especially in combination with thiazide diuretics in patients with diabetes mellitus and metabolic syndrome. However, the recommendations of 2013, presented at the congress of the European Society of Cardiology for hypertension in June 2013 made amendments on β blockers, which have vasodilating properties. Among such drugs are called celiprolol, nebivolol, carvedilol and (Mancia G. *et al*., 2013) [11]. Advantage of using nebivolol is proved as compared with other beta-blockers, in particular bisoprololum, IHD patients in their effect on platelet aggregation (Chen S. *et al*., 2015) [13].

Due to above described properties of nebivolol, it's useful to analyze / study its effects on the spectrum of essential amino acids in the blood serum of patients with unstable angina, in comparison with other β adrenoceptor - bisoprololum.

Purpose of the study

Compare the effectiveness of antianginal therapy, which includes bisoprolol with antianginal therapy, which consists of nebivolol in the treatment of essential amino acids balance disorders in the blood serum of patients with unstable angina (UA).

Material and Methods

The study involved 68 unstable angina (UA) patients aged 65 to 76 years (average age of patients was 68,2 ± 6,3 years). The patients were divided into two groups: 35 people treated kardiket, bisoprolol, Atoris, Enap, aspirin, clopidogrel, and 38 people, which include Nebivolol therapy. All study group patients were statistically homogeneous and comparable. (UA) diagnosis was made on the basis of the order/protocol of the Ministry of Health of Ukraine dated 03.07.2006, № 436 "On Approval of the provision of medical care protocols, specialty" Cardiology ". The survey did not include patients with heart failure IIB and stage III, atrial fibrillation, concomitant diseases in the stage of decompensation, cancer, diseases of the musculoskeletal system.

For the objective investigation of amino acid, blood serum was used. We used the method of ion-exchange liquid-chromatography column. In the blood plasma, the following was determined: non-essential amino acid (AA): ornithine, taurine, aspartic acid, serine, glutamic acid, proline, glycine, alanine, cysteine, tyrosine, glutamine.

The research results were processed on the PC using Microsoft Office software package. Statistical analysis of the data used, Microsoft Excel 2010. The significance of differences between the average performance of different groups was detected by using Student's t-test or Pearson criteria.

Results and discussion

Comparing the results of treatment in patients treated with various beta-blockers, it can be concluded that no significant difference in the dynamics of the total amount of non-essential (AA) serum as compared with before treatment, and with the index control group(CG) have been identified (all < 0.05).

It should be noted that the intake of nebivolol in patients with UA compared to the CG had normalized ornithine levels in serum (*P*> 0.05), which is not observed in the application of bisoprololum (p <0.05). This AA is a substrate of arginase - an enzyme that is present everywhere in living organisms, and synthetize NO (Vorobets Z.D. *et al*, 2012) [2]. Therefore, these changes may be interpreted as compensating destabilization under the coronary circulation.

It is essential to note that after the treatment of patients receiving nebivolol, normal levels of taurine were observed as compared to the CG (p> 0.05), and the patients receiving bisoprolol, the findings did not change significantly compared to either CG or in comparison to before treatment (both p <0.05). Taurine in myocardial amino acid constitute for about 50% (Kharchenko N.V. *et al*, 2014) [10], hence the normalization of metabolism of AA may be treated as a defensive response in terms of coronary circulation disorders.

The level of aspartic acid in the blood serum of both groups revealed no significant changes (all p> 0.05).

Noteworthy is the fact that patient's antianginal therapy which include Nebivolol, serine levels increased significantly as compared with before treatment to 1.56 mg / mol / 100 ml (p <0.05), although it remained significantly lower at 3.25 u / mol / 100 ml compared to the CG (p <0.05). Patients taking bisoprolol, significant dynamics on the level of the AA did not happen (all p <0.05). It should be noted that the form of the serine protease serine - enzymes which, besides its other functions, play an important role in the blood coagulation cascade reactions. Members of this group of proteases are for example thrombin, trypsin, VIIa factors, IXa, Xa, XIa, XIIa, and protein C. Therefore, this increase in the level of AA in serum during treatment with nebivolol can improve the rheological properties of the blood of patients with UA.

A significant increase in glutamic acid levels in UA patients receiving nebivolol compared to the pre-treatment at 5.72 mg / mol / 100 ml (p <0.05), although compared with the CG it remains significantly lower at 5.97 microns / mol / 100 ml (p <0.05). UA patients, which includes therapy bisoprolol, glutamic acid levels did not change significantly as compared with before treatment (p <0.05) and remained significantly lower at 13.12 mg / mol / 100 ml compared to the CG (p <0, 05).

It is known that glutamic acid reacts with ammonia, converting it to neutralize toxic glutamine. Also essential is that this increases the AA muscle cell membrane permeability to potassium ions, which contribute to increase in strength of muscle contraction and the muscle force of contraction of the myocardium in particular.

Patients on both treatment groups after treatment significantly decreased proline serum respectively 4.74 mg / mol / 100 ml (p <0.05) and 3.39 mg / mole / 100ml (p <0.05) but remained significantly lower compared to the CG, respectively, at 8.5 mg / mole / 100ml (p <0.05) and 19.85 mg / mol / 100 ml (p <0.05).

Interesting was dynamics of change of glycine in blood serum in patients with UA. Patients taking bisoprolol, level of AA had increased significantly as compared with before treatment and 4.28 kg, respectively, mg / mol / 100 ml and 5.29 mg / mole / 100ml (both p <0.05), and in patients whose therapy included nebivolol, glycine levels significantly decreased as compared with before treatment and 11.2 kg, respectively mg / mol / 100 ml and 10.9 mg / mole / 100ml (both p <0.05).

Since myocardial ischemia reduces oxygen level, which leads to an increase in the generated cytotoxic superoxide anion radicals and other forms of reactive oxygen, there is a sharp irreversible inhibition of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, it is possible reception of glycine as a cytoprotector in acute myocardial ischemia (MI) can lead to a decrease in lesion myocardial cells during hypoxia (Krasnenkova T.P. *et al*, 2014) [7]. Reducing the level of glycine in the blood serum of patients with UA during treatment with nebivolol indicates an increase in intracellular metabolism of the AA, which means a protective response in a violation of the coronary circulation.

Revealed the same changes in alanine serum levels in both groups after treatment. Patients taking bisoprolol, level of this AC significantly decreased as compared with before treatment and CG respectively 14.48 mg / mol / 100 ml (p <0.05) and 5.16 mg / mole / 100ml (p 0, 05), and in patients whose therapy included nebivolol respectively 23.72 mg / mol / 100 ml (p <0.05) and 14.1 mg / mole / 100ml (p <0.05).

We also identified the same dynamic changes of serum levels of cysteine in both groups after treatment. Patients taking bisoprolol, level of AA had increased significantly as compared with before treatment and 5.01 kg, respectively, in the u / mol / 100 ml (p <0.05), and 3.79 mg / mole / 100ml (p <0.05), and in patients whose therapy included nebivolol - by 3.62 mg / mol / 100 ml (p <0.05), and 2.4 mg / mol / 100 ml (p <0.05).

UA patients taking bisoprolol, tyrosine level was significantly reduced by 3.92 mg / mol / 100 ml as compared with before treatment (p <0.05) and 3.28 mg / mole / 100ml compared to the CG (p < 0.05) and in patients whose therapy included nebivolol, the level of the AK was not significantly changed compared to the pre-treatment and compared to the CG (both p> 0.05).

Because tyrosine, with the participation of vitamins B and C, folic and pantothenic acid, and a number of trace elements in the human body is synthesized Coenzyme Q10. Coenzyme Q10 effectively protects the lipids of biological membranes and blood lipoprotein particles (phospholipids - "membrane glue") from destructive processes peroxidation, DNA and protects the body from oxidative modification of proteins by the accumulation of reactive oxygen species (Korovina N.A., Ruuhe E.K., 2002) [6]. More than 20 years of experience in clinical trials of coenzyme Q10 in thousands of patients convincingly prove his role in the pathology of cardiovascular deficiency, which is not surprising, because in heart muscle cells the most large energy needs. The protective role of coenzyme Q10 due to its participation in the processes of energy metabolism and

antioxidant properties of cardiomyocytes (Kapelko V.I., 2003) [4]. Retention normal serum NS tyrosine patients when using nebivolol can be regarded as a positive therapeutic effect in a destabilization of the coronary circulation.

Table 1: The amino acid spectrum of blood serum in patients during treatment with UA, bisoprololum and nebilet Micromole/ 100ml (M ± m)

Amino Acids	Before treatment (I)	After the treatment. (Bisoprolol) (II)	After the treatment. (Nebivolol) (III)	PI-II	PI-III
Ornithine	17,64±1,24	11,66±0,96	12,65±1,2	*P* <0,05	*P* <0,05
Taurine	5,60±0,05	5,77±0,37	8,32±0,08	*P*>0,05	*P* <0,05
Aspartic acid	2,63±0,04	2,26±0,21	2,34±0,05	*P*>0,05	*P*>0,05
Serine	13,94±0,08	15,06±0,71	15,5±0,54	*P*>0,05	*P* <0,05
Glutamic acid	10,99±0,07	9,52±0,77	16,67±0,9	*P* <0,05	*P* <0,05
Proline	8,18±0.08	12,92±0,77	11,57±0,66	*P* <0,05	*P* <0,05
Glycine	32,85±1,3	37,13±1,55	21,65±0,43	*P* <0,05	*P* <0,05
Alanine	55,85±2,1	41,37±1,24	32,13±1,33	*P* <0,05	*P* <0,05
Cysteine	5,60±0,06	10,61±0,82	9,22±0,07	*P* <0,05	*P* <0,05
Tyrosine	7,18±0,08	3,04±0,15	5,99±0,08	*P* <0,05	*P* <0,05
Glutamine	37,79±1,5	53,67±2,14	54,86±2,15	*P* <0,05	*P* <0,05
Total	198,35±9,7	203, 01±11,12	190,9±9,15	*P*>0,05	*P*>0,05

Table 2: The amino acid spectrum of blood serum in patients during treatment with UA, bisoprololum and nebilet compared to the CG Micromole / 100ml (M ± m)

Amino Acids	CG (I)	After the treatment		P (II-III)	P(II-IV)
		Bisoprolol	Nebilet		
Ornithine	14,36±1,2	11,66±0,96	12,65±1,2	P <0,05	P <0,05
Taurine	9,02±0,44	5,77±0,37	8,32±0,08	P>0,05	P>0,05
Aspartic acid	2,12±0,06	2,26±0,21	2,34±0,05	P>0,05	P>0,05
Serene	18,75±1,43	15,06±0,71	15,5±0,54	P <0,05	P <0,05
Glutamic acid	22,64±1,16	9,52±0,77	16,67±0,9	P <0,05	P <0,05
Proline	21,42±1,27	12,92±0,77	11,57±0,66	P <0,05	P <0,05
Glycine	31,84±2,24	37,13±1,55	21,65±0,43	P <0,05	P <0,05
Alanine	46,53±1,31	41,37±1,24	32,13±1,33	P <0,05	P <0,05
Cysteine	6,82±0,31	10,61±0,82	9,22±0,07	P <0,05	P <0,05
Tyrosine	6,32±0,08	3,04±0,15	5,99±0,08	P <0,05	P>0,05
Glutamine	51,89±2,45	53,67±2,14	54,86±2,15	P>0,05	P>0,05
Total	231,71±10,9	203,1±11,12	190,9±9,15	P <0,05	P <0,05

It should be noted that patients in both treatment groups after treatment returned to normal levels of glutamine (both $p < 0.05$). UA patients, both study groups, antianginal therapy did not significantly affect the total amount of non-essential AA. After the treatment, the amount of nonessential AA remained significantly lower compared to the CG, respectively, 28.6 mg / mole / 100ml ($p < 0.05$) and 40.8 mg / mole / 100ml ($p < 0.05$). Thus, the inclusion of anti-anginal therapy with nebivolol compared with bisoprololum effective influence in the correction of disorders of blood plasma amino acids levels in patients with UA.

Conclusions

1. As a result of carried out treatment/study, no significant difference between the readings in the total amount of non-essential AA were detected by the two groups of patients receiving nebivolol & bisoprolol
2. UA patients receiving antianginal therapy with nebivolol, had normalized the level of ornithine, AA which takes part in the disposal of ornithine cycle.
3. UA patients receiving nebivolol, normalized levels of taurine, has cardio-protective properties. With the usage of bisoprololum, the level of this particular AA was not significantly changed.
4. UA patients on antianginal therapy, including nebivolol resist normal levels of tyrosine, which can serve as a compensatory response in a destabilization of the coronary circulation.
5. UA patients treated with antianginal therapy, which included bisoprolol and during treatment with antianginal therapy, which included nebivolol, had normalized levels of glutamine.

References

1. Bulanova EL, Drapkina OM. Nebivolol as inducer of nitric oxide synthesis. Difficult patient, 2014; 10:30-34.
2. Vorobets ZD, Yefremova UP, Yakubets OI. Arginase system in the human organism in the development of pathological processes. Clinical and Experimental Pathology. 2012; XI,3(41),2:153-160.
3. Ivashkin VT, Drapkina OM. Clinical significance of nitric oxide and heat shock proteins. M.: GEOTAR-Media, 2001, 88.
4. Kapelko VI. Reactive oxygen species, antioxidants and prevention of heart diseases. Russian Medical Journal, 2003; 11(21):1185-1188.
5. Kovalenko VM, Sirenko Yu M, Nesukai OH. The method of application nebilet for the treatment of cardiac

insufficiency. Information letter Ministry of Healthcare of Ukraine, № 1, 2007. «Internal Medicine».- 2007; 1(1).
6. Korovina NA, Ruuhe EK. The use of coenzyme Q10 in prevention and treatment. Application of the antioxidant drug Kudesan (Coenzyme Q10 with Vitamin E) in cardiology. Cardiology, 2002; 12:51-55.
7. Krasnenkova TP, Yevseyenko AS, Kuvshinova NA. The efficiency of glycine at the experimental model of acute myocardial ischemia. Medical Journal. 2014; 2:70-73.
8. Moshkovska Yu O. Nebivolol – a third generation β-blocker: the advantages and prospects of application in medical practice. Medicines Ukraine. 2015; 4(190):42-46.
9. Nasyrova AG. Nitric oxide in the mechanisms of regulation of the pumping function of the heart in rats. Dissertation on completion. Art. MD Kazan. 2004, 131.
10. Kharchenko NV, Anokhina HA, Kharchenko VV. Peculiarities of nutrition patients with non-alcoholic steatohepatitis in combination with hypertrophic cardiomyopathy. The journal Health of Ukraine, 2014; 27(03):38-39.
11. Authors/Task Force Members, Mancia G, Fagard R, Narkiewicz K *et al*. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 4(28):2159-219.
12. Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. Physiol. Rev. 2003; 83(1):59-115.
13. Chen S, Fu AC, Jain R, Tan H. Cardiovascular-related healthcare resource utilization and costs in patients with hypertension switching from metoprolol to nebivolol. Am. Health Drug Benefits. 2015; 8(2):71-80.