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PHARMACOTHERAPY EFFICACY AND SAFETY CRITERIA BASED ON SPECTRAL SHIFTS IN ELDER PATIENTS WITH ARTERIAL HYPERTENSION AND CORONARY ARTERY DISEASE

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Abstract

The article is dedicated to development of homeostatic criteria of efficacy and safety of drugs combinations “lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid”. These criteria are based on study of homeostatic shifts and their association with clinical and laboratory parameters on elder patients with arterial hypertension (AH) II, III stage combined with coronary artery disease (CAD).

Complex clinical, biochemical, biophysical and instrumental investigation was performed in 67 patients with AH II, III stage combined with CAD.

On the grounds of developed criteria was established that for patients with AH II and CAD is not recommended combination “lisinopril, acetylsalicylic acid” and for those ones with AH III and CAD prohibited combinations “lisinopril, bisoprolol, acetylsalicylic acid” and “lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid” in order to prevent development of drug induced renal dysfunction.

It was also determined safety of combinations “lisinopril, bisoprolol, acetylsalicylic acid”; “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” for patients with AH II and CAD and “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” for those ones with AH III and CAD.

Key words: **pharmacotherapy, efficacy, safety, arterial hypertension, coronary artery disease, laser correlation spectroscopy.**

Introduction

Arterial hypertension (AH) and coronary artery disease (CAD) prevail among all cardio-vascular diseases namely in elder patients – 41.8% and 38.3%. This comorbidity increases risk of mortality and complications: myocardial infarction, stroke, heart failure [1].

Choice of effective and safe pharmacotherapy (PT) is not easy because of different comorbid diseases in these patients and peculiarities of pharmacokinetics and pharmacodynamics. Elder patients have retardation of absorption and spreading of drugs, decrease of their biotransformation pace, slow elimination [2]. These patients have more often complications after PT, untypical reactions, frequent hemodynamic disorders [3].

Low treatment efficacy and high risk of complications caused by PT is a reason to seek for informative methods of diagnostics and evaluation of treatment influence in elderly. Laboratory methods which allow hold polysystemic estimation of homeostatic state and take into consideration intermolecular interactions in the blood components are able to decide this challenge [4].

One of such methods is laser correlation spectroscopy (LCS) [5]. This method allows reveal such blood components as proteins, which transport drugs and low density lipoproteins, which take part in atherogenesis process. And it is wide known that one of the theories of AH and CAD development is presence of atherosclerotic changes in coronary arteries, aorta and its branches [6]. But its possibilities in prognosis of side effects during treatment and evaluation of PT influence on homeostatic shifts are not studied and investigated enough in elder patients with cardiac comorbidity.

So, the investigation **object** was to study homeostatic criteria of efficacy and safety on the background of different antihypertensive combinations influence and their association with traditional clinic and biochemical data in elderly with AH II, III stages combined with CAD.

Material and methods

107 patients with PH II, III stages combined with CAD were examined and treated in therapeutic department of Centre of reconstructive and restorative medicine (University Clinic). Their mean age was 70.8±7.5 years. Diagnosis was based on clinical, laboratory and instrumental data according to ESH/ESC recommendations [7]. Besides obligatory

investigation methods vegetative index Kerdo (VIK) was calculated in the investigation by formula [8]:

VIK = 1-(d/p)*100, where d – is diastolic blood pressure (DBP) and p – heart rate (HR) in one minute. Glomerular filtration rate (GFR) was also calculated according to MDRD formula [9].

All patients were divided into 2 groups: group I (n=51) – those ones with AH II stage and CAD, group II (n=57) – patients with AH III stage and CAD.

Patients of the group I received 3 variants of the combined PT: variant Ia – "lisinopril, acetylsalicylic acid" (n=19); Ib – "lisinopril, bisoprolol, acetylsalicylic acid" (n=11); Ic – "lisinopril, bisoprolol, indapamide, acetylsalicylic acid" (n=20).

Patients of the group II were prescribed also 3 variants of the combined PT: variant IIa – "lisinopril, bisoprolol, acetylsalicylic acid" (n=19); IIb – "lisinopril, bisoprolol, indapamide, acetylsalicylic acid" (n=20); IIc – "lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid" (n=17).

Monitoring during PT was for 14 days of the patients stay in therapeutic department. In this period of time all proper laboratory and instrumental investigations were carried out and blood serum for LCS was taken.

The special laboratory method for estimation of serum homeostatic features was LCS. It helps to measure spectral characteristics of the induced monochromatic coherent radiation in biological liquids. That makes possible to register particles with hydrodynamic radius 1 - 10000 nanometers. Results are presented as a histogram [5].

According to previous studies [10], to the I zone (0-10 nanometers) are included low-molecular monomeric albumins and glycolipid free complexes; to the II zone (11-30 nanometers) are included globulin proteins and low-molecular lipoprotein complexes; to the III zone (31-70 nanometers) are included high-molecular lipoprotein complexes, RNP-, DNP molecules, the low-molecular immune complexes; to the IV zone (71-150 nanometers) are included mainly constitutive immune complexes of the average size. Huge particles (≥ 150 nanometers, the V zone) are present in patients with allergization.

Investigation of blood serum by mean of LCS was made using the technique developed by prof. Bazhora Yu.I. and prof. Noskin L.A. [11]. Blood serum was taken on the 2^{nd} and 14^{th} day of the treatment.

Obtained results were calculated with statistics parametric and nonparametric methods. Data were presented as mediana, 25^{th} and 75^{th} percentile [12].

Results

In the group AH II with CAD prescription of combination "lisinopril, acetylsalicylic acid" caused stabilization of systolic blood pressure (SBP) and DBP in target borders recommended for elderly (below 150/90 mm Hg) and HR on the 2nd day of PT. This combination led to growth of creatinine level by 18.0 mcmol/l and decrease of GFR by 22.2 ml/min/1,73m^2 on the 10th day of treatment ($p<0,05$). So, combination "lisinopril, acetylsalicylic acid" causes development of drug induced renal dysfunction.

Under the influence of combination "lisinopril, bisoprolol, acetylsalicylic acid" SBP reached recommended rates on the 1st day of treatment, while vegetative nervous regulation (VNR) was shifted towards direction of pathological parasympatheticotonia (VIK = -42.8 units). Such a dynamic of VNR can be connected with neuromodulatory action of bisoprolol.

Combination "lisinopril, bisoprolol, indapamide, acetylsalicylic acid" caused lowering of SBP and DBP to target levels on the 2nd day of PT. VNR in this group was normally directed – physiological parasympatheticotonia.

Data on subfractional redistribution in blood serum and directions of spectral shifts under the influence of combinations Ia, Ib, Ic in the group I presented in tables 1 and 2.

Table 1

Dynamic of subfractional redistribution in blood under the influence of combinations Ia, Ib, Ic in the group AH II and CAD

DDZ, %	Used combination of drugs					
	Combination Ia		Combination Ib		Combination Ic	
	before PT	during PT	before PT	during PT	before PT	during PT
I (0-10 nm)	4 (1,5; 12,5)	3 (0; 10)	3 (1; 5)	7 (2,5; 11)	5,5 (2,7; 9,2)	3 (1; 9,5)
II (11-30 nm)	13 (7; 31)	21 (11; 29)	17 (13; 19)	22 (14; 30)	24,5 (16; 38,2)	18,5 (5; 31,5)
III (31-70 nm)	25 (5,5; 47)	31 (24; 47)	24 (23,5; 43)	33 (23,5; 36,5)	20 (11; 42)	18,5 (0; 30,5)
IV (71-150 nm)	25 (11; 51,5)	25 (0; 33*)	22 (0; 45)	20 (7,5; 42,5)	28,5 (13,2; 41,5)	28,5 (16,2; 66,7*)
V (>150 nm)	4 (0; 18,5)	0 (0; 2)	13 (1; 46)	8 (0; 16*)	6 (0; 22)	6 (0; 25)

Remark: *- $p<0,05$ after PT vs before PT; DDZ – discrete dynamic zone; combination Ia: "lisinopril, acetylsalicylic acid"; Ib: "lisinopril, bisoprolol, acetylsalicylic acid"; Ic: "lisinopril, bisoprolol, indapamide, acetylsalicylic acid".
Data presented as mediana; 25th and 75th percentile in the brackets.

Table 2

Directions of spectral shifts under the influence of combinations Ia, Ib, Ic in the group AH II and CAD

Type of homeostatic direction, %	Used combination of drugs					
	Ia		Ib		Ic	
	before PT	during PT	before PT	during PT	before PT	during PT
Normological	5,3	15,4	0	9,1	0	6,2
Hydrolytic	36,8	46,2	27,2	45,4*	40	31,4
Anabolic	42,1	38,4	54,6	27,3*	45	50
Mixed	15,8	0*	18,2	18,2	15	12,4

Remark: *- $p<0,05$ after PT vs before PT.

Under the influence of studied combinations there were not any statistical changes in LCS data of subfractional redistribution. At the same time 75th percentile showed significant decrease of particles with diameter 71-150 nm by 18.5% after prescription of combination “lisinopril, acetylsalicylic acid”, lowering of particles above 150 nm by 30.0% at the background of combination “lisinopril, bisoprolol, acetylsalicylic acid” and growth of particles with diameter 71-150 nm after usage of combination “lisinopril, bisoprolol, indapamide, acetylsalicylic acid”.

Dynamic of homeostatic shifts under the influence of combination “lisinopril, acetylsalicylic acid” was following: decrease of mixed type by 15.8%. Usage of combination “lisinopril, bisoprolol, acetylsalicylic acid” led to growth of hydrolytic type by 18.2% with simultaneous lowering of anabolic one by 27.3%. After prescription of combination “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” was observed prevalence of anabolic type among all other homeostatic spectral shifts.

Growth of creatinine level under the influence of combination “lisinopril, acetylsalicylic acid” was associated with decrease of particles with diameter of 71-150 nm ($r = -.70$). Lowering of VIK rate after prescription of combination “lisinopril, bisoprolol, acetylsalicylic acid” correlated with decrease of particles with diameter above 150 nm ($r = +.52$). Decline of SBP rate at the background of combination “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” associated with growth of particles with diameter 71-150 nm ($r = -.73$).

In the group AH III with CAD SBP and DBP reached target borders on the 2nd day of treatment at the background of combinations “lisinopril, bisoprolol, acetylsalicylic acid” and “lisinopril, bisoprolol, indapamide, acetylsalicylic acid”. Combination “lisinopril, bisoprolol,

indapamide, isosorbide dinitrate, acetylsalicylic acid" caused stabilization of SBP, DBP and HR on recommended rates on the 2nd day of PT. Combination "lisinopril, bisoprolol, acetylsalicylic acid" led to shift of VNR towards direction of pathological parasympatheticotonia (VIK = -24.0 Units).

Combinations "lisinopril, bisoprolol, acetylsalicylic acid" and "lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid" induced growth of blood creatinine level by 22.5 mcmol/l and 31.0 mcmol/l and decrease of GFR by 25.4 ml/min/1,73m^2 and 18.5 ml/min/1,73m^2.

Combinations "lisinopril, bisoprolol, indapamide, acetylsalicylic acid" and "lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid" caused appearance of microalbuminuria (0.1 g/l).

Results on subfractional redistribution in blood serum and directions of spectral shifts under the influence of combinations IIa, IIb, IIc in the group II presented in tables 3 and 4.

Table 3

Dynamic of subfractional redistribution in blood under the influence of combinations IIa, IIb, IIc in the group AH III and CAD

DDZ, %	Used combination of drugs					
	Combination IIa		Combination IIb		Combination IIc	
	before PT	during PT	before PT	during PT	before PT	during PT
I (0-10 nm)	6 (2,5; 13)	5 (2; 11,8)	7 (2; 15,8)	6 (1,8; 12)	5 (1; 17)	7 (4; 11,5)
II (11-30 nm)	16 (11,5; 48)	23,5 (13; 30,8)	31,5 (20,8; 41,8)	14,5* (10,3; 34,8)	24 (12; 52)	32 (11; 39)
III (31-70 nm)	24 (16; 35,5)	21 (5,3; 32,3)	16,5 (7,3; 28,5)	17,5 (0; 29)	13 (4; 22)	27* (13,5; 32)
IV (71-150 nm)	12 (6,5; 41,5)	38,5* (9,5; 54,3)	12 (6,8; 24,3)	32* (11; 43,5)	17 (4; 32)	19 (10; 42)
V (>150 nm)	2 (0; 12,5)	11,5 (0; 19,3)	7 (0; 30)	12,5 (5,5; 32,8)	7 (0; 38)	0 (0; 15)

Remark: *- p<0,05 after PT vs before PT; combination IIa: "lisinopril, bisoprolol, acetylsalicylic acid"; Ib: "lisinopril, bisoprolol, indapamide, acetylsalicylic acid"; Ic: "lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid". Data presented as mediana; 25th and 75th percentile in the brackets.

Table 4

Directions of spectral shifts under the influence of combinations Ia, Ib, Ic in the group AH II and CAD

Type of homeostatic direction, %	Used combination of drugs					
	Ia		Ib		Ic	
	before PT	during PT	before PT	during PT	before PT	during PT
Normological	10,5	11,1	10,0	9,1	0,0	6,3
Hydrolytic	52,7	27,8*	55,0	45,4	35,4	31,2
Anabolic	31,5	27,7	20,0	27,3	47,0	50,0
Mixed	5,3	33,4*	15,0	18,2	17,6	12,5

Remark: *- $p<0,05$ after PT vs before PT.

Under the influence of combination “lisinopril, bisoprolol, acetylsalicylic acid” in subfractional redistribution was observed increase of particles with diameter of 71-150 nm by 26.5% according to LCS data. Combination “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” caused decrease of particles with diameter 11-30 nm with simultaneous increase of 71-150 nm particles. Combination “lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid” induced growth of particles with diameter of 31-70 nm by 14%.

Homeostatic shifts after prescription of combination “lisinopril, bisoprolol, acetylsalicylic acid” were characterized by increase of mixed type by 28.1% and decrease of hydrolytic one by 24.9%. Two other combinations didn’t cause any significant changes in direction of spectral shifts.

Increase of creatinine level under the influence of combination “lisinopril, bisoprolol, acetylsalicylic acid” associated with decrease of hydrolytic type of homeostatic shifts ($r = -.53$) and growth of mixed one ($r = +.62$) and at the background of combination “lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid” it is correlated with increase of particles with diameter of 31-70 nm ($r = +.68$). Lowering of DBP while prescribing combination lisinopril, bisoprolol, indapamide, acetylsalicylic acid” associated with decrease of particles with diameter 11-30 nm ($r= +.59$) and reduce of SBP correlated with growth of particles with diameter 71-150 nm ($r = -.66$).

Conclusions

Studied by mean of LCS molecular mechanisms and homeostatic shifts in blood serum under the influence of different pharmacotherapy combinations allowed develop homeostatic criteria of treatment efficacy and safety in elder patients with AH combined with CAD. These

criteria correlate with traditional biochemical and hemodynamic parameters.

Revealed homeostatic shifts which associated with development of drug induced renal dysfunction in patients with AH II, III with CAD can be useful for maintaining of PT safety. Changes of LCS parameters which associated with renal dysfunction developed before increase of creatinine level. That fact can be crucial for PT correction at time.

According to developed criteria for patients with AH II and CAD is not recommended combination “lisinopril, acetylsalicylic acid” and for patients with AH III and CAD – combinations “lisinopril, bisoprolol, acetylsalicylic acid” and “lisinopril, bisoprolol, indapamide, isosorbide dinitrate, acetylsalicylic acid” in order to prevail drug induced renal dysfunction.

It is also determined safety and efficacy of combinations “lisinopril, bisoprolol, acetylsalicylic acid”; “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” for patients with AH II and CAD and combination “lisinopril, bisoprolol, indapamide, acetylsalicylic acid” for patients with AH III and CAD.

Obtained data can be used for choice of optimal pharmacotherapy in elderly with AH combined with CAD and prevent progress of treatment side effects. So, LCS can be recommended as an informative method of clinical pharmacology for usage in clinical practice.

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