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DISORDERS OF NEUROMEDIATOR POOL IN PATIENTS WITH MULTIFOCAL ATHEROSCLEROSIS

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In 62 patients with multifocal atherosclerosis of men of average age (72.3±3.3) years, blood flow parameters in peripheral arteries, serotonine, histamine, dophamine, beta–endorphins in serum and serotonine in plasma. Found a significant decrease in volumetric blood flow in the arteries carotis interna, mesenterica superior, femoralis communis, tibialis posterior; the levels of serotonine, histamine, dophamine in the serum significantly exceeded their maximum values of almost healthy individuals (control group, n=19), respectively, 4.6, 4.3 and 3.5 times. Taking cilostazol for 12 weeks contributed to a significant ($p<0.001$) increase in volumetric blood flow in the studied arteries: – in arteries carotis interna by 18.2 %, in arteria mesenterica superior – by 17.8 %, in arteria femoralis communis – by 18.8 %, in arteria tibialis posterior – by 69.4 %, which was accompanied by an improvement in the clinical manifestations of the disease, a significant decrease plasma serotonine level (by 2.9 times; $p<0.001$) and serotonine (by 39.0 %; $p<0.05$) and histamine (by 62.1 %; $p<0,01$) in blood serum, increase beta–endorphin level (by 29.8 %; $p<0,01$). Serum dophamine levels did not change significantly. The role of neurotransmitters in the course of multifocal atherosclerosis is discussed; the pharmacotherapeutic possibilities of cilostazol are analyzed.

Key words: multifocal atherosclerosis, serotonine, histamine, dopamine, b-endorphin, hemodynamics, cognitive function, myocardial ischemia.

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ПОРУШЕННЯ НЕЙРОМЕДІАТОРНОГО ПУЛУ У ХВОРИХ НА МУЛЬТИФОКАЛЬНИЙ АТЕРОСКЛЕРОЗ

У 62 хворих на мультифокальний атеросклероз чоловічої статі середнім віком (72.3±3.3) років досліджено показники кровотоку в периферичних артеріях, рівні серотоніну, гістаміну, дофаміну, бета-ендорфіну в сироватці та серотоніну в плазмі крові. Виявили значне зменшення об'ємного кровотоку в артеріях carotis interna, mesenterica superior, femoralis communis, tibialis posterior; рівні серотоніну, гістаміну, дофаміну в сироватці крові достовірно перевищували їх максимальні значення практично здорових осіб (контрольна група, n=19) відповідно в 4.6, 4.3 та 3.5 рази; Прийом цилостазолу впродовж 12 тижнів сприяв достовірному ($p<0.001$) збільшенню об'ємного кровотоку в досліджуваних судинах: – в arteria carotis interna на 18,2 %, в arteria mesenterica superior – на 17,8 %, в arteria femoralis communis – на 18,8 %, в arteria tibialis posterior – на 69,4 %, що супроводжувалось поліпшенням клінічних проявів захворювання, достовірним зниженням рівня серотоніну в плазмі (в 2.9 рази; $p<0.001$) та серотоніну (на 39.0 %; $p<0.05$) і гістаміну (на 62.1 %; $p<0.01$) в сироватці крові, підвищенням вмісту бета–ендорфіну (на 29.8 %; $p<0.01$). Рівень дофаміну в сироватці крові достовірно не змінився. Обговорюється роль нейромедіаторів в перебігу мультифокального атеросклерозу, аналізуються фармакотерапевтичні можливості цилостазолу.

Ключові слова: мультифокальний атеросклероз, серотонін, гістамін, дофамін, b-ендорфін, гемодинаміка, когнітивна функція, ішемія міокарда.

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The problem of generalized-multifocal atherosclerosis (MAS), i.e. simultaneous damage to the arteries of two or more vascular territories, remains insufficiently studied [5, 6]. Patients with MAS have more severe and varied manifestations of the disease and significant changes in neurohumoral balance, than persons with a lesion of one vascular territory [5, 8, 11, 14]. It is known that a number of humoral factors, such as histamine (H), serotonin (5-HT), beta-endorphin (b-E), dopamine (D) and others are aimed at adapting organs to the physiological needs of the body. With ischemic lesions of vital organs, there is an increase in the level of some neurotransmitters, both in the affected organ and in the circulating blood. Thus, in ischemic stroke (IS) the level of 5-HT and D increases by 3–4 times in both cerebrospinal fluid and blood plasma [2, 10], in patients with acute myocardial infarction (MI) the level of b-E in the blood plasma by 20 times, and the levels of 5-HT and H are almost by 3–4 times higher than those of healthy individuals [11]. Changes in neurohormone levels in ischemic lesions of the muscles of the legs and intestines are less studied and understood.

In MAS, the presence of ischemic changes simultaneously in several organs and systems can affect the balance of neurotransmitter secretion and have an unintended effect. In addition, numerous data indicate

a paradoxical effect of altered concentrations of neurotransmitters on the endothelium and arterial vessels affected by atherosclerotic process [10]. It is known that at too high concentrations of 5-HT can cause uncontrolled hypotension and bradycardia, which can lead to serious consequences [13]. At present, the connection between the level of neurotransmitters in the blood in patients with MAS with impaired blood supply to organs and the effectiveness of treatment has not been sufficiently studied.

Antiplatelet agents play an important role in improving blood supply in atherosclerotic lesions of the arteries. Despite the numerous data on the effectiveness of cilostazol (C) in the treatment of intermittent claudication syndrome (ICS), in patients after coronary and carotid artery stenting [2, 5, 7, 12], its effect on blood levels of 5-HT, H, D and b-E, volumetric blood flow in arteries affected by atherosclerosis remains insufficiently studied [2]. There are virtually no studies of the effectiveness of C in patients with ICS as a manifestation of MAS.

The purpose of the study was to access changes in the neurohumoral pool (serotonine, histamine, dophamine and beta-endorphin) and blood flow in various vascular territories in patients with multifocal atherosclerosis, and to evaluate the pharmacotherapeutic potential of cilostazol in the treatment of such patients.

Materials and methods. The 12-week open-label randomized clinical trial included 62 male patients (72.3±3.3) years with clinical and hemodynamic signs of atherosclerosis of four vascular territories (coronary, cerebral, mesenteric and femoral) – MAS group. The control group (CG) consisted of 19 almost healthy men aged (69.5±4.5) years. All patients signed an informed consent to participate in the study.

Criteria for inclusion in the study: men aged≥60 years; intermittent claudication syndrome (ICS); presence of a history of myocardial infarction and/or coronary revascularization (CR); suffered an ischemic stroke or transient ischemic attack (TIA) for more than 12 months ago.

Exclusion criteria: taking anticoagulants or antiplatelets, except acetylsalicylic acid, a high risk of thromboembolism and/or bleeding; thrombocytopenia, life-threatening arrhythmias, congestive heart failure, severe hepatic and/or renal impairment, cilostazol intolerance.

Randomization and intervention. Patients with MAS were randomized into two subgroups – MAS–C and MAS–B – in a ratio of 1:1, taking into account the age of patients (<70 or≥70 years) as a stratification factor. The initial examination was performed on the background of basic therapy (the same in subgroups). All patients included in the study had a clinical examination, daily Holter ECG monitoring (HM ECG) on the Cardio SenseK "HAI-MEDICA", dopplerography (ALOKA, Arietta S70) – a.carotis interna (CIA), a.mesenterica superior (MSA), a.femoralis communis, a.tibialis posterior (TPA) – maximum/peak systolic velocity (PSV) and volumetric blood flow velocity (VF), intima-media complex thickness (KIM) were determined, and resistance index (RI) was calculated. All patients were determined ankle-brachial index (ABI) [5]. Studies of cognitive function were performed by using the Montreal Cognitive Assessment (MoCA) Test [4]. The level of plasma 5-HT was determined by ion exchange chromatography (IOC) [3]. The level of 5-HT, H, b-E and D in the serum was determined by enzyme-linked immunosorbent assay (ELISA) [1]. Painless distance (PWD) and maximum walking distance (MWD) were assessed in MAS patients. After the initial examination, patients of the MAS-C subgroup in addition to the basic therapy for 12 weeks took C ("plestazol" manufactured by the Kiev Vitamin Plant) 100 mg 2 times a day; patients of the MAS–B subgroup received only basic therapy. Patients of subgroups MAS–C and MAS–B were examined again after 12 weeks of treatment.

Statistical analysis was performed using the computer program IBM SPSS, version 23, MedStat. The normality of the distribution of data was performed by the Shapiro–Wilk method. The nature of the distribution of variables was assessed using the Kolmogorov–Smirnov test for one sample. At normal distribution, the arithmetic mean of the indicator (M) and the standard deviation (±SD) were calculated. With a different than normal distribution of data, the median was calculated, using the first and third quartiles (Me (Q1; Q3). When comparing the values under the condition of normal data distribution, Student`s t-test was used; the method of pairwise sampling was used to determine the reliability of the dynamics of indicators. The difference between the data was considered significant at $p<0.05$.

Results of the study and their discussion. The mean age of patients in the subgroups MAS–C and MAS–B was, respectively, (72.8±3.8) and (71.5±3.9) years, patients who had MI were 48 % (15/31) and 45 % (14/31), persons with coronary revascularization (CR) – 68 % (21/31) and 71 % (22/31), IS – 71 % (22/31) and 65 % (20/31), TIA – 29 % (9/31) and 35 % (11/31), hypertension had 42 % (13/31) and 39 % (12/31), compensated diabetes – 29 % (9/31) and 32 % (10/31) persons respectively.

At the initial examination, the values of volumetric blood flow in all studied vessels of patients MAS–C and MAS–B were significantly lower than in CG, and did not differ significantly between

subgroups (Table 1). Taking of C for 12 weeks contributed to a significant improvement in blood flow in the studied arteries - a significant (p<0.001) increase in VF in TPA (by 46.7 %), FCA (18.8 %), MSA (17.8 %), CIA (at 18.2 %). Significant dynamics of the studied blood flow parameters (VF, MnV, PSV) in patients of the MAS–B subgroup was not detected. The thickness of KIM in the studied arteries during the observation period in the both subgroups has not changed.

Table 1

Parameters of blood flow in the studied arteries of CG (n=19) and subgroups MAS–C (n=31) and MAS–B (n=31) before and after three weeks of treatment

Measurements	Groups of patients	Studied arteries			
		CIA	MSA	FCA	TPA
PSV, sm/sec	CG	73.4 (62.1;83.7)	57.5 (48.6;79.4)	69.8 (58.6;83.2)	47.3 (38.6;65.2)
	MAS–C initial examination	141.4 (126.8;156.2)##	84.3 (72.6;93.7)##	78.4 (69.5;89.7)##	85.4 (76.4;97.5)##
	MAS–C after 12 weeks of treatment C	127.9** (118.7;148.0)	73.8** (47.9;59.8)	74.8 (68.7; 81.5)*	74.6** (58.9;83.1)
	MAS–B initial examination	142.7 (124.3;157.4)##	85.1 77.4;97.5)##	77.5 (63.8;87.5)##	86.2 (77.5;95.8)##
	MAS–B re–examination	142.4 (123.7;162.1)	84.9 (76.5;98.4)	76.4 (64.3;88.2)	85.8 (77.4;93.2)
VF, ml/min	CG	242.8 (198.4;252.6)	168.2 (152.7;187.3)	198.5 (172.6;216.3)	12.7 (8.9;14.4)
	MAS–C initial examination	186.5 (173.5;197.2)###	74.3 (59.6;83.5)###	87.4 (72.7;98.7)###	4.5 (3.2;5.7)###
	MAS–C After 12 weeks of treatment C	220.4 (162.8;237.1)***	87.5 (77.1;92.8) ***	103.8 (83.2;106.4) ***	6.6 (5.1;7.2)***
	MAS–B initial examination	187.3 (172.4;198.3)###	76.4 (61.5;84.8)###	88.2 (74.3;92.6)###	4.7 (3.3;5.4)###
	MAS–B re–examination	187.8 (173.5;192.4)	78.2 (62.5;85.3)	88.4 (73.5;91.4)	4.8 (3.2;5.6)
RI, c.u.	CG	0.78 (0.67;0.89)	0.83 (0.75;0.92)	0.88 (0.81;0.93)	0.82 (0.79;0.95)
	MAS–C initial examination	0.93 (0.79;0.98)	0.96 (0.82;0.99)	0.95 (0.82;0.97)	0.94 (0.78;0.96)
	MAS–C after 12 weeks of treatment C	0.91 (0.89; 0.95)	0.96 (0.94;1.01)	0.96 (0.93;1.11)	0.96 (0.95;0.99)
	MAS–B initial examination	0.92 (0.81;0.97)	0.97 (0.83;0.98)	0.94 (0.84;0.98)	0.95 (0.77;0.98)
	MAS–B re–examination	0.91 (0.80;0.96)	0.97 (0.87;0.99)	0.95 (0.84;0.96)	0.96 (0.83;0.98)

Note. PSV – maximum systolic velocity; RI – resistance index; VF –volumetric blood flow. The difference between the values of the indicator compared to CG is significant: # – p<0.05; ## – p<0.01; ### – p <0.001; The dynamics of the indicator during treatment is significant: * – p <0.05; ** – p<0.01; *** – p<0.001.

As it can be seen from table 2, patients in subgroups MAS–C and MAS–B during the initial examination revealed significantly (p<0.001) higher levels of 5-HT in serum and 5-HT, H and D in the plasma of patients compared with CG. Thus, in the serum, in the subgroups MAS–C and MAS–B, respectively, the level of 5-HT was 4.6 and 4.7 times, H – 4.3 and 4.2 times, D – 3.5 and 3.5 times higher than similar values of CG, and the level of 5-HT in blood plasma – by 7.8 and 7.7 times, respectively. Serum b–E levels in patients of subgroups MAS–C and MAS–B were by 14.5 and 12.7 % lower (p<0.05), respectively, than in patients with CG.

After 12 weeks of C on the background of basic therapy in the subgroup MAS–C observed a significant decrease in the level of 5-HT and H in the serum, respectively, by 39.0 % (p<0.05) and 62.1 % (p<0.01), the plasma 5-HT level – by 2.9 times (p<0.001). However, their level remained higher than that of CG individuals. The level of D in the serum under the influence of C did not change significantly, and the level of b–E increased by 29.8 % (p<0.01). Significant changes in the level of neurotransmitters in the blood of patients of the subgroup in MAS–B were not observed.

In patients of the MAS–C subgroup, a 12-week course of C contributed to a reduction in the clinical manifestations of ICS – pain, paraesthesia and weakness in the muscles of the lower extremities, a significant (p<0.01) increase in walking distance – PWD by 76.8 % (from 172.5±41.3 to 305.1±21.2 m),

MWD by 42.5 % (from 395.1±90.2 to 563.1±44.2 m). In the subgroup MAS–B the subjective signs of ICS and PWD and MWD did not change significantly.

Under the influence of 12-week taking C according to the daily HM EGC significantly decreased the number of PEIM (from 5.7±0.3 to 3.9±0.3; p<0.001) due to episodes with both elevation (p<0.05) and depression (p<0.001) segment ST, PlEIM (from 8.11±0.67 to 6.26±0.55; p<0.03), as well as their average duration (from 4.1±0.5 to 3.7±0.4 min; p<0.05). The data obtained indicate a positive effect of C on coronary blood flow. Our data correspond to the results of a multicenter study of the effectiveness of C in patients with vasospastic angina [12]. In the subgroup MAS–B significant changes in the indicators of HM ECG were not detected (p=0.2).

Table 2

Dynamics of the level of humoral factors in the blood of patients of subgroups MAS–C and MAS–B before and after 12 weeks of treatment (M±SD).

Measurements	Control group	MAS			
		MAS–C		MAS–B	
		initial examination	after 12 weeks of treatment C	initial examination	after 12 weeks
	n=19	**n=31**	**n=31**	**n=31**	**n=31**
Serotonine (plasma), μg/ml	1.85±0.13	14.35±1.21 ###	4.91±0.53 *** #	14.67±0.51 ###	14.34±0.62 ###
Serotonine (serum), c.u.	0.41±0.17	1.87±0.11 ###	1.14±0.08 * ##	1.92±0.09 ###	1.90±0.12 ###
Histamine, c.u.	0.31±0.02	1.32±0.17 ###	0.50±0.02**#	1.31±0.11 ###	1.31±0.13 ###
Dophamine, c.u.	0.42±0.04	1.48±0.15 ###	1.36±0.13 ##	1.47±0.09 ###	1.39±0.11 ###
Beta–endorphine, c.u.	0.55±0.07	0.47±0.07 #	0.61±0.06 ** #	0.48±0.06 #	0.47±0.04 #

Note. The difference between the values of the indicator compared to CG is significant: # – p <0.05; ## – p <0.01; ### – p <0.001; the dynamics of the indicator is significant in the treatment process: * – p <0.05; ** – p <0.01; *** – p <0.001.

After 12 weeks of C, most patients (86.3 %, 27/31) of the MAS-C subgroup noted a decrease in the frequency and intensity of episodes of headache and dizziness, including positional, as well as some improvement in memory. At the beginning of the study, the average score of MoCA in them was (19.22±0.52) points, at re–examination – (19.86±0.47) points (p=0.01), that indicates an improvement in cognitive function. Significant dynamics of MoCa score in the subgroup MAS–B was not detected.

According to the data obtained in patients with MAS, the decrease in VF in the studied arteries is accompanied by a significant (p<0.001) increase in the levels of 5–HT, H and D in the blood compared with CG. It is known that a significant increase in 5-HT and H leads to increased vasospastic reactions, increased permeability of vascular walls, platelet aggregation and the formation of new atheromatous plaques [10, 14]. Significant increases in plasma and serum 5-HT levels can cause significant bradycardia and uncontrolled decreases in BP [13]. H activates the transformation of macrophages into foam cells and the formation of new atheromatous plaques [14]. In the presence of organ ischemia, D acts as a counterparty to 5–HT and H. It is known that its concentration increases in ischemic stroke, and the course of stroke is directly related to changes in the concentration of D in blood plasma and cerebrospinal fluid [9]. In addition, D inhibits the transformation of arterial smooth muscle fibroblasts into foam cells [15].

As shown by our study, the addition to the recommended set of pharmacological drugs C provides a significant reduction in blood 5-HT and H – by 39.0 % (p<0.05) and 62.1 % (p<0.01). On the background of increased VF (p<0.001) in all studied arteries FCA, TPA, CIA and MSA, reduced clinical manifestations of lower extremity ischemia, the number and duration of episodes of myocardial ischemia, improved cognitive function. A significant decrease in the serum H level – factor, which stimulates the formation of foam cells in the arterial wall, indicates the presence of C antiatherogenic properties. This coincides with the data of other studies [2, 14]. Taking C for 12 weeks did not significantly affect the level of D and significantly increased the level of b-E in patients of the subgroup MAS–C (p<0.01).

Thus, C, reducing the extremely high aggressive levels of 5-HT and H, and virtually without changing the high level of D and increasing the level of b-E, changes the ratio of 5-HT and H to D and b–E, in favor of antisclerotic and antithrombotic mechanisms, which also improves blood flow in vessels affected by atherosclerosis, reduces the signs of ischemia of the relevant organs and clinical manifestations of the disease.

Conclusions

1. In patients with MAS with clinical manifestations of atherosclerotic lesions of the cerebral, coronary, mesenteric and femoral arterial territories on the background of a significant decrease in volumetric blood flow there is an increase serum 5-HT – by 4.6 times, H – by 4.3 times , D – by 3.5 times compared with their content in the blood of almost healthy people of comparable age.

2. Addition of cilostazol to the basic therapy of patients with MAS led to improvement of their clinical condition - reduction of pain in the lower extremities when walking, increase in painful and painless walking distances, reduction in the number of episodes of myocardial ischemia (according to daily ECG monitoring), improving cognitive function (increasing the average MoCa score).

3. Taking cilostazol (on the background of basic therapy) increased volumetric blood flow in all affected arteries (FCA, CIA, MSA TPA), a significant decrease in serum levels of 5-HT and H (respectively 39.0 %; $p<0.05$ and 62.1 %; $p<0.01$) and an increase in the level of b-E by 29.8 % ($p<0.01$); without significant changes in D level. This changes the ratio of 5-HT and H to D and b-E, in favor of antisclerotic, antithrombotic mechanisms, which improves blood flow in vessels affected by atherosclerosis, reduces signs of ischemia of relevant organs and clinical manifestations of the disease.

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