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Research Article

Meteoprotective Properties of Melaxen in Old and Middle Aged Patients with Ischemic Heart Disease in Combination with Arterial Hypertension

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ABSTRACT

We studied 102 patients (mean age 60.1±3.3 years) with arterial hypertension (AH) II-III stage, grade 2-3 and ischemic heart disease (exertional angina functional class (FC) I-II, postinfarction cardiosclerosis). The control group of patients received traditional therapy (TT): beta -blockers, calcium channel blockers, ACE inhibitors, antiplatelet agents, diuretics and nitrates. The dates of 24-hours BP monitoring (24-hours BPM) before and after treatment were subjected to correlation analysis with meteorological factors, the values of which were obtained from the server "Weather Russia" (meteo.infospace.ru). Similar studies were conducted in patients receiving drugs with adaptogenic effect (melaxen) on the background of the TT. We drew attention to the changes of circadian rhythm and blood pressure variability in the studied patients on the background of the effects of weather on the main hemodynamic parameters. At baseline circadian rhythm with low blood pressure reduction at night and increased variability were found in the majority of studied patients. TT insignificantly reduces the amount of correlation between blood pressure and weather factors, reduces the effect of air temperature and dew point in the state of hemodynamics, but does not reduce the magnetosensitivity of the patients. This normalization of the circadian rhythm is not observed, the variability in systolic blood pressure (SBP) was significantly reduced in the daytime at this group of patients. The treatment with the inclusion melaxen reduces the number and degree of correlation between blood pressure and the meteorological factors (eg, atmospheric pressure, cloud cover top), as well as indices of geomagnetic activity. It is accompanied by a normalization of the circadian rhythm and significant decrease in the variability of systolic and diastolic blood pressure (DBP) at night. Thus, melaxen has the most pronounced meteoprotective properties, promotes the normalization of the circadian rhythm, variability, recommended for meteosensitive patients with arterial hypertension and ischemic artery disease.

Keywords: arterial pressure, variability, circadian rhythm, meteorological factors, arterial hypertension, ischemic heart disease, melaxen.

INTRODUCTION

Recent years studies have confirmed that the lack of adequate night time blood pressure (BP) reduction is a powerful independent risk factor for death from cardiovascular disease (CVD). A linear relationship was established between mortality from CVD and the degree of BP reduction during the night. Each increase in the ratio of night to day (for systolic blood pressure (SBP) or diastolic blood pressure (DBP) by 5% was associated with an increase in the risk of death by 20%, and this ratio was maintained even in those cases when the mean values for blood pressure did not exceed the norm for 24 hours (135/80 mm Hg). It was found that the lack of adequate blood pressure lowering at night is associated with increased involvement in the pathological process of target organs and may be a useful (albeit non-specific) indicator of secondary forms of arterial hypertension (AH) [1, 2]. Patients with hypertension are characterized by increased rigidity of the arteries, which leads to a decrease in the elasticity of the wall, the loss of the ability of the arteries to smooth pulse waves and ultimately to increase the variability of blood pressure. The effect of increased variability of blood pressure on the risk of complications in hypertension (myocardial infarction and stroke) was detected as far back as the 1990-2000s [3, 4]. In the ASCOT study, the significance of variability in blood pressure as a predictor of cerebrovascular and coronary events with AH was demonstrated [5]. At present, there are practically no data on the effect of meteorological factors on the indices of 24-hours BP monitoring (24-hours BPM), changes in variability, diurnal rhythm in patients with AH and ischemic heart disease (IHD) in the context of treatment with adaptogenic preparations. Actual is the study of the relationship between weather factors and blood pressure, as well as changes in the variability of blood pressure, daily rhythm against the background of therapy in patients with high cardiac risk.

The aim of the study is to study the influence of weather factors on the indices of 24-hours BPM, changes in variability and diurnal rhythm in old and middle aged patients with AH and IHD in the background of traditional therapy and with the use of drugs with melaxen.

RESEARCH METHODOLOGY

The first group of patients with stage II-III AH, 2-3 degrees in combination with IHD (angina pectoris I-II FC, Post infarction Cardio sclerosis) and receiving TT, consisted of 50 people (mean age was 59.2±2.9 years). Traditional antihypertensive and antihypertensive therapy included ACE inhibitors (perindopril 5-10 mg 1 p / day), diuretics (hydrochlorothiazide 12.5-25 mg / day once), calcium antagonists (amlodipine 2.5-10 mg 1p / day), and beta-blockers (Bisoprolol 2.5-10 mg 1p / day), antiplatelet agents (aspirin at a dose of 125 mg once in the evening) and nitrates (monocinque at a dose of 20 mg twice daily) with anginal attacks.

The second group included 52 patients (mean age 57.8±2.9 years) receiving complex therapy with melaxen. Traditional therapy included the same drugs that patients in the first group received, as well as melaxen (melatonin, Unipharm, Inc., USA) at a dose of 3 mg at 22 hours.

24-hour blood pressure monitoring was performed using a portable device "BR-102 Schiller" (Switzerland). This method allows you to judge the average daily values of blood pressure, its daily profile, episodes of critical increase and the relationships of the observed parameters [6-8].

The mean daily heart rate (HR), SBP, DBP, pulse BP (PBP), average BP (ABP), DP (double product) were determined by the results of 24-hours BPM; day and night SBP and DBP (dSBP, dDBP and nSBP, nDBP). The variability of blood pressure (VBP) was assessed by the standard method in terms of the standard deviation from the average blood pressure (standard deviation - STD). STD SBP and STD DBP were analyzed at day and night. The value of the pressure load was calculated time index (TI) percentage of time during which the values of the BP exceed the critical ("safe") level. We studied day TI time SBP and TI DBP percent of blood pressure measurements exceeding 140 and 90 mm Hg. In the period of wakefulness, as well as nocturnal STD SBP and STD DBP percent of blood pressure measurements above 120 and 70 mm Hg in the period of sleep. In addition, the indicator of morning dynamics was determined the morning rise (DMR) BP value in the period from 4 to 10 hours in the difference between the maximum morning and minimum night systolic and diastolic blood pressure. The daily rhythm was estimated the degree of night decrease (DND) of BP the decrease in SBP and DBP at night with respect to their daytime level [1, 9, 10]. According to the DND, the daily rhythm of patients was determined: "dippers", "non-dippers", "over-dippers", "night-peakers".

Taking into account the purpose and objectives of this study, the work assesses the influence of weather factors: atmospheric pressure, air temperature, relative humidity, dew point, cloudiness, wind direction and speed, and geomagnetic activity (Kr-index) on the state of the cardiovascular system. A correlation analysis of 24-hour blood pressure monitoring indices before and after the course of treatment and weather factors during the measurement, on the eve of the study, on the next day, and also taking into account the weather parameters was carried out. Meteorological factors were obtained from the Weather Russia server (meteo.infospace.ru). The influence of meteorological conditions on the human body, suffering from meteorological dependence, is an occasion for a careful study of the reactions formed in response to the effect of meteorological factors and the creation of protective measures against "meteotropic reactions" in particular in patients suffering from AH and IHD [11-14, 17]. In connection with this, we searched for drugs that have an adaptogenic effect in the form of correction of the adverse effect of weather factors on the hemodynamic parameters of patients with AH and IHD. Medicines (melaxen,) which have adaptogenic effect, but are poorly studied as drugs used to prevent meteorological dependence have been selected within the framework of this study. Melaxen (melatonin) - the neurohormone of the epiphysis - possesses unique adaptative possibilities; it is a corrector of endogenous rhythms relative to exogenous rhythms of the environment [15, 16].

Statistical processing of the data was carried out using Microsoft Excel 2003, Statistica (v 6.0), SPSS for Windows (v.13,0) and the R × S computer program (Rows × Columisis). The presence of a statistical relationship between the main indicators of hemodynamics and weather parameters was determined by the level of significance of Pearson's linear correlation coefficients.

RESULTS AND DISCUSSION

Under the influence of TT, reliable positive dynamics of the main indicators of 24-hour blood pressure monitoring in most patients was noted. The dynamics of hemodynamic parameters was manifested by a decrease in daily HR values from 78.7±1.5 to 75.8±1.4 beats / min (p<0.04), SBP from 157.9±2.4 to 147.4±2.7 mm Hg (p<0.008), DBP from 95.2±0.9 to 91.9±1.4 mm Hg (p<0.05), the arterial pressure from 115.8 to 1.3 to 110.8 1.3 mm Hg (p<0.01), the ABP from 62.9±1.9 to 56.9±2.2 mm Hg (p<0.003). Day and night values of SBP decreased from 162.9±2.5 to 153.6±2.1 mm Hg (p<0.007) and from 148.7±2.5 to 141.0±2.6 mm Hg (p<0.01), respectively. TI SBP decreased in the afternoon from 74.2±2.6 to 65.4±3.1% (p<0.02) and at night from 72.4±2.9 to 64.9±3.2% (p<0.04). VBP SBP decreased from 62.9±1.5 to 58.1±1.9 mm Hg (p<0.03). DBP significantly decreased from 98.2±1.1 to 95.9±0.9 mm Hg (p<0.05) only in the daytime.

The daily profile of the SBP of the first group of patients before the treatment was presented by "dippers" (50%), "non-dippers" (46%) and "night-peakers" (4%). The degree of DBP reduction was sufficient in 26% of cases ("dippers"), insufficient in 58% ("non-dippers"), 2% (over-dippers) and inverted at 14% ("night-peakers"), Against the background of traditional therapy, despite the antihypertensive effect, the normalization of the circadian rhythm of BP was not observed. The daily profile of the SBP for TT is represented by "dippers" (30%), "non-dippers" (68%) and "night-peakers" (2%). The daily profile of the DBP is presented by "dippers" (30%), "non-dippers" (60%) and "night-peakers" (10%). It should be noted that under the influence of TT, the DND of the SBP and the DBS of the DBP did not practically change.

A decrease in the variability of SBP in the daytime was revealed from 18.4±0.5 to 15.9±0.7 mm Hg (p<0.004) (Table 1). The dynamics of daytime STD DBP, as well as nocturnal STD SBP and STD DBP indicators indicate their lack of significant changes.

Table 1: Influence of traditional therapy on blood pressure variability

Indicators	**Before treatment (n = 50) (M±m)**	**after treatment (n = 50) (M±m)**	**P<**
Day STD SBP, mm Hg.	18.4±0.5	15.9±0.7	**0.004****
STD DBP, mm Hg.	15.2±0.6	14.2±0.5	0.08
Night STD SBP, mm Hg.	16.0±0.6	14.7±0.5	0.07
STD DBP, mm Hg.	12.6±0.3	11.9±0.3	0.09

Correlation links between hemodynamic parameters and weather factors before and after TT have been revealed according to 24-hour blood pressure monitoring data. Initially, 30 reliable weak and moderate degrees of correlation were identified, which indicate the interaction of blood pressure indicators with the parameters of meteorological and geomagnetic activity (Tables 2, 3). Prior to treatment, the greatest influence on blood pressure was provided by the air temperature and dew point. Most susceptible to the effects of weather are PBP and ABP. The characteristic time of the shift in the reaction of the organism relative to the measurement time of meteofactors varies greatly and corresponds to an advance of 1 hour or a delay of 2 hours.

Table 2: Correlation relationship between hemodynamics parameters and weather factors in patients with arterial hypertension and ischemic heart disease receiving traditional treatment, according to the 24-hours BPM (p<0.001)

	Before treatment			**After treatment**	
	SBP	**DBP**	**Pulse**	**SBP**	**DBP**
Atmosphere pressure:	-	-	-	-	-
Temperature: - one hour before measurement	 0.310				
Relative humidity:	-	-	-	-	-
Dew point: - one hour before measurement - 2 hours after measurement - 3 hours after measurement	 0.340 0.314 0.322				
Clouds upper:	-	-	-	-	-
Direction of the wind:	-	-	-	-	-
Wind speed:	-	-	-	-	-
Index of geomagnetic activity (Kr-index): At the time of measurement - one hour before measurement - 2 hours after measurement					 0.317 0.315 0.305

At TT, the number of correlations between BP and weather factors was 27, while the degree of correlation between the parameters studied did not decrease. Influence of air temperature and dew point decreased, but the number of correlation links with the indicators of cloudiness, atmospheric pressure, relative humidity and geomagnetic activity increased. ABP is most vulnerable to weather.

Table 3: Correlation relationship between hemodynamics parameters and weather factors in patients with AH and IHD receiving traditional treatment, according to the 24-hours BPM (p<0.001)

	Before treatment			**After treatment**	
	PBP	**ABP**	**DP**	**PBP**	**ABP**
Atmosphere pressure: At the time of measurement - one hour before measurement - 2 hours before measurement - 3 hours before measurement - 2 hours after measurement			 0.315 - 0.424 - -		
Temperature: At the time of measurement - one hour before measurement -One hour after measurement - 2 hours after measurement - 3 hours after measurement	 0.370 0.426 0.303 0.339 0.343	 0.406 0.443 0.359 0.376 0.378			 0.344 0.405 - 0.311 -
Relative humidity: - 2 hours before measurement - 3 hours before measurement -fall				 - - 0.318	 0.399 0.329 -
Dew point: At the time of measurement - one hour before measurement - 2 hours before measurement - 3 hours before measurement -One hour after measurement - 2 hours after measurement - 3 hours after measurement	 0.339 0.403 - - 0.300 0.344 0.357	 0.398 0.464 0.305 - 0.388 0.421 0.435			 0.376 0.455 0.374 0.360 0.330 0.373 0.388

Clouds upper: At the time of measurement - 3 hours before measurement - 3 hours after measurement -fall				0.349 0.400 - 0.367	
Clouds average: -fall	-	-	-	0.464	-
Direction of the wind:	-	-	-	-	-
Wind speed: - one hour before measurement	0.376				
Index of geomagnetic activity (Kp-index): - one hour before measurement - 2 hours after measurement		0.305 0.401			- 0.321

Thus, TT slightly reduces the number of correlation links between BP and weather factors, reduces the effect of air temperature and dew point on the state of hemodynamics, but does not reduce the magnetosensitivity of patients with AH and IHD.

The addition of melaxen in TT resulted in a positive dynamics of the 24-hours BPM indices in the majority of patients. Changes in hemodynamic parameters were manifested by a significant decrease in daily SBP values from 154.4±2.7 to 140.9±1.9 mm Hg (p<0.001), DBP from 92.8±1.4 to 83.5±1.3 mm Hg (p<0.001), the PBP from 62.3±1.4 to 57.3±1.4 mm Hg (P<0.001), and also ABP from 112.5±1.1 to 103.0±3.1 mm Hg (p<0.002). The parameters of heart rate and DP have statistically significantly decreased from 76.6±1.2 to 73.7±1.4 beats / min (p<0.05) and from 117.1±2.4 to 103.3±4.1 conv. units (p<0.01), respectively.

Daytime and night values of SBP decreased from 160.2±2.6 to 146.9±2.3 mm Hg (p<0.001) and from 150.2±2.1 to 130.9±2.3 mm Hg (p<0.001), respectively. There was a decrease in DBP in the afternoon from 96.2±1.4 to 89.1±1.3 mm Hg (p<0.001) and DBP values at night from 89.1±1.3 to 78.8±1.5 mm Hg (p<0.001).

TI SBP in the daytime hours significantly decreased from 72.5±3.7 to 46.8±4.8% (p<0.002) and at night from 74.9±3.9 to 56.5±3.3% (p<0.002). TI DBP also decreased day and night from 67.9±3.1 to 54.3±2.8% (p<0.002) and from 64.5±4.1 to 46.4±3.2% (p<0.002), respectively. VBP SBP and DBP did not statistically reliably change.

DND SBP increased from 6.6±0.7 to 11.0±0.9% (p<0.002), DND DBP - from 7.8±0.7 to 12.0±0.9% (p<0.002) only under the influence of treatment with melaxen.

Addition to therapy with melaxen allows not only to lower the level of blood pressure, but also to normalize its daily profile. Before the therapy, the degree of nocturnal decline in SBP was sufficient in 23% of cases ("dippers"), insufficient in 71% ("non-dippers") and inverted "night-peakers" (6%). The daily profile of the DBP was presented by "dippers" (38%), "non-dippers" (56%) and "night-peakers" (6%). After treatment with melaxen, the number of "dippers" of SBP increased to 63%, the number of "non-dippers" of SBP decreased to 37%; The number of "dippers" DBP increased to 61%, "non-dippers" DBP decreased to 37%, revealed 2% "over-dippers" DBP.

By studying the variability of blood pressure before and after treatment with melaxen, it was established that STD SBP was significantly decreased from 17.1±0.5 to 14.5±0.6 (p<0.001) and STD DBP from 14.0±0.5 to 12.1±0.6 (p<0.004) at night Table 4.). The day-to-day BP variability indicators have changed unreliably.

Table 4: Influence of treatment with melaxen on blood pressure variability

Indicators	**Before treatment (n=52) (M±m)**	**After treatment (n=52) (M±m)**	**P<**
Day STD SBP, mmHg. STD DBP, mmHg	16.0±0.6	14.4±0.8	0.07
	14.1±0.5	13.1±0.5	0.07

Night STD SBP, mmHg.	17.1±0.5	14.5±0.6	0.001***
STD DBP, mmHg	14.0±0.5	12.1±0.6	0.004**

Correlation links between hemodynamic parameters and weather factors before and after therapy with melaxen inclusion according to 24-hours BPM data were revealed. 30 reliable correlation bonds of weak, medium and high degree, which testify to the interaction of blood pressure indicators with the parameters of meteorological and geomagnetic activity, were initially identified. Prior to treatment, the greatest influence on BP was provided by the indices of atmospheric pressure, upper cloud cover, and geomagnetic activity (Table 5, Table 6). The PBP values are most prone to weather influence. Meteo factors have just slight influence on the parameters of SBP, DBP and heart rate both before and after treatment. The characteristic time of shift of the reaction of the organism relative to the moment of meteorological factors measurement varies greatly and corresponds to a zero time shift (the instant of measurement) and an advance by 1 hour.

Table 5: Correlation relationship between hemodynamics parameters and weather factors in patients with AH and IHD receiving therapy with melaxen, according to the 24-hours BPM (p<0.001)

	Before treatment			**After treatment**	
	SBP	**DBP**	**Pulse**	**SBP**	**DBP**
Atmosphere pressure: At the time of measurement	0.303				
Temperature:	-	-	-	-	-
Relative humidity:	-	-	-	-	-
Dew point:	-	-	-	-	-
Clouds upper: - one hour before measurement			0.363		
Clouds average:	-	-	-	-	-
Wind direction:	-	-	-	-	-
Wind speed: - 2 hours before measurement			0.319		
Geomagnetic activity index (Kr-index):	-	-	-	-	-

In the treatment with melaxen, the number of correlations between BP and weather factors was 22, while the degree of interrelation between the parameters studied decreased. The influence of atmospheric pressure, cloud cover and geomagnetic activity decreased. There were no correlations between SBP, DBP, heart rate and weather factors. PBP, ABP, DP are approximately equally affected by weather.

Table 6: Correlation relationship between hemodynamics parameters and weather factors in patients with AH and IHD receiving therapy with melaxen, according to the 24-hours BPM (p <0.001)

	Before treatment			**After treatment**	
	PBP	**ABP**	**DP**	**PBP**	**ABP**
Atmosphere pressure:					
At the time of measurement	0.510	0.466	-	0.319	0.403
- one hour before measurement	0.501	0.502	-	0.408	0.401
- 2 hours before measurement	0.600	0.501	-	-	-
- 3 hours before measurement	0.468	0.378	-	0.311	-
-One hour after measurement	-	-	-	-	-
- 2 hours after measurement	0.379	-	-	0.401	-
- 3 hours after measurement	-	-	-	0.308	-
-fall	-	-	0.396	-	-
Temperature:					
-fall			0.381		
Relative humidity:					
At the time of measurement	-	-		0.313	0.303
- one hour before measurement	-	-		0.301	0.309
-One hour after measurement	0.384	0.396		0.302	0.301
Dew point:	-	-	-	-	-
Clouds upper:					

At the time of measurement - one hour before measurement -One hour after measurement - 2 hours after measurement			0.340 0.330 0.332 0.335		
Clouds average: At the time of measurement - one hour before measurement	 0.370 -		 - 0.301		
Direction of the wind: At the time of measurement -fall	 0.352 -			 - 0.300	 - 0.294
Wind speed: - 3 hours after measurement	 0.358	 0.304			
Index of magnetic activity (Kr-index): At the time of measurement - one hour before measurement - 3 hours before measurement -fall	 0.343 0.386 0.347 -	 - 0.371 - -	 - - - 0.315		

Thus, treatment with the addition of melaxen in patients with stage II-III AH, 2-3 degrees and coronary artery disease reduces the number and degree of correlation between BP and meteorological, geomagnetic factors according to 24-hour blood pressure monitoring.

CONCLUSIONS

1. According to 24-hours BPM, hypotensive effect of TT is established in the form of a decrease in SBP in daytime and night time, DBP in daytime, decrease in PBP, ABP and HR. Correlation analysis between the data of 24-hours BPM and weather factors after TT indicates a decrease in the influence of air temperature, dew point on hemodynamics, some increase in the magneto sensitivity of patients. Estimating the effect of TT on BP variability in day and night hours, a significant decrease in variability of SBP during the day was revealed. Despite the hypotensive effect, the normalization of the circadian rhythm of BP was not observed.
2. According to 24-hours BPM, a more pronounced antihypertensive effect of therapy with melaxen in the form of a decrease in SBP, DBP in day and night hours, a decrease in PBP and ABP, heart rate, DP, normalization of the daily profile of blood pressure was established. The correlation analysis between the 24-hours BPM data and weather factors after TT with melaxen showed a decrease in the effect of atmospheric pressure, upper cloud cover and the absence of geomagnetic activity influence on blood pressure. A significant decrease in the variability of SBP and DBP during night hours was established.

REFERENCES

1. Achmetzyanova, E.H. 2006. Methodical aspects of determining the type of circadian rhythm according to daily monitoring of blood pressure. Russian Cardiology Journal, 3: 49-53. (in Russian)
2. Rogoza A.N., Agaltsov, M.V., Sergeeva, M.V. 2005. 24-hours blood pressure monitoring: options for medical opinions and comments. Nizhny Novgorod: DECOM, 64 p. (in Russian)
3. Fratolla, A. Parati, G., Cuspidi, C. 1993. Prognostic value of 24-hour pressure variability. J. Hypertens., 11: 1133-1137
4. Mancia, G. 2012. Short-and long-term blood pressure variability: present and future. Hypertension, 60: 512-517.
5. Rothwell, P.M. 2010. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure and episodic hypertension. Lancet, 375: 895-905.
6. Golikov, A.P., Lukyanov, M.M. 2002. Using the daily monitoring of blood pressure and heart rate in patients with a combination of hypertension and coronary heart disease. Bulletin arrhythmology, 27: 27-28. (in Russian)
7. Efremova, O.A., Nikitin, V.M., Lipunova, E.A., Kochetkova I.A, Kamyshnikova L.A. 2014. Visualization and virtual diagnosis of the cardiovascular system current state by

the results of its non-invasive monitoring. Research Journal of Pharmaceutical, Biological and Chemical Sciences: RJPBCS, 5(5): 1000-1005.

8. Johansson, J.K. 2012. Prognostic Value of the Variability in Home-Measured Blood Pressure and Heart Rate: The Finn-Home Study. Hypertension, 59: 212-218
9. Efremova, O.A., Nikitin V.M., Mitin M.S., Lipunova EA., Kamyshnikova L.A. 2015. Early diagnosis of coronary heart disease risk by the expert automated system based on the results of heart rate variability analysis. Research Journal of Medical Sciences, 9 (4): 240-244.
10. Grassi, G., Bombelli, M., Brambilla, G. 2012. Total cardiovascular risk, blood pressure variability and adrenergic overdrive in hypertension: evidence, mechanisms and clinical implications. Curr Hypertens Rep., 14: 333-338.
11. Revich, B.A., Shaposhnikov, D.A. 2008. Climatic conditions, air quality and mortality of Moscow population 2000-2006. Institute of national economy forecasting of the Russian Academy of Sciences, 102-141. (in Russian)
12. Savenkov, M.P., Ivanov, C.N., Cafonova, T.E. 2007. Pharmacological correction of meteopatic reactions in patients with arterial hypertension. Difficult patient, 5(3): 17-20. (in Russian)
13. Schroeder, K., Fahey T., Ebrahim S. 2004. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch. Intern. Med., 164(7): 722-732.
14. Halberg, F., Cornélissen, G., Regal, P. 2004. Chronoastrobiology: proposal, nine conferences, heliogeomagnetics, transyears, near-weeks, near-decades, phylogenetic and ontogenetic memories. Biomedicine and Pharmacotherapy: 4th International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 58 (1): 150-187.
15. Zaslavckaya, R.M., Shcherban, E.A., Logvinenko, S.I. 2008. Melatonin in complex treatment of patients with stable angina and arterial hypertension. Clinical medicine, 86(9): 64-67. (in Russian)
16. Shcherban, E.A., Zaslavckaya, R.M., Logvinenko, S.I., Storozhenko, S.Yu., Morozova I.A. 2015. State of hemodynamics in patients with arterial hypertension and ischemic heart disease on the on the background traditional treatment in combination with melatonin. Belgorod State University Scientific Bulletin. Medicine Pharmacy, 22(219): 33-38. (in Russian)
17. Shcherban, E.A., Zaslavskaya, R.M., Logvinenko, S.I., Morozova, I.A., Gridneva, A.S. 2016. Influence of weather conditions on the indicators of central and peripheral hemodynamics in patients with arterial hypertension and ischemic heart disease. Belgorod State University Scientific Bulletin. Medicine Pharmacy, 12(233): 43-49. (in Russian)