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The effect of combined pharmacotherapy on the dynamics of cardiog hemodynamics and cardiac pacing variability in patients with arterial hypertension

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Abstract
Dynamic observation and treatment of 145 patients with stage II arterial hypertension has been performed. Approbation therapy included a comparison of the effectiveness of the use of basic antihypertensive therapy, an additional use of the drug magnesium or mebiker or their simultaneous administration. It is proved that the use of magnesium medication contributes to a significant decrease in the daily average systolic and diastolic blood pressure. An additional appointment of the mebiker coincides with the sympathetic and parasympathetic links of the autonomic nervous system. Consequently, the appointment of proven pharmacological agents has pathogenetic justification and is appropriate in patients with arterial hypertension stage II.

Keywords: arterial hypertension, cardiac rhythm variability, systolic blood pressure, diastolic arterial pressure, magnesium medication, mebiker

Introduction
Arterial hypertension (AH) is one of the most common diseases in the world. Numerous studies indicate the need for early detection of hypertension and its timely correction [1] to prevent adverse cardiovascular events [2]. The risk of cardiovascular complications in patients with hypertension depends not only on the absolute level of blood pressure, but also on fluctuations in blood pressure over different time periods, the so-called variability of blood pressure (BP) [3]. OJSC is a result of complex interaction of external environmental and behavioral factors and internal cardiovascular regulatory mechanisms, which have not yet been fully studied [4]. The analysis of the heart rate variability (HRC) allows to objectively evaluate the status of various parts of vegetative regulation, including those involved in the regulation of the frequency of heart rate and blood pressure. As a rule, progression of hypertension is accompanied by a decrease in HRV [5]. Determinants of the variability of BP have been studied in several population surveys: most often they include age, arterial pressure, heart rate, gender, and regulatory changes from the central and peripheral nervous system, concomitant diseases [6, 7]. Investigation of the mechanisms responsible for the severity of changes in blood pressure, confirmed the leading role of nerve regulation (central nervous system, baroreceptor reflex) in this process. It is believed that the dynamics of BP during the day occurs under the influence of the central and autonomic nervous system and is associated with different types of daily activity. One of the methods for assessing the regulatory influence of the autonomic nervous system is the study of heart rate variability (HRV). It should be noted that the spectral analysis of HRV has a particular advantage, providing an opportunity to evaluate the absolute contribution of sympathetic and parasympathetic modulating effects on the regulation of the sinus node [8].

In view of this, there is the expediency of finding drugs that would optimize traditional antihypertensive therapy by influencing some of the pathogenetic links of regulatory destabilization.

Microelement magnesium (Mg2+) is important oligoelementss that controls the normal functioning of cardiomyocytes, provides a cycle of systole diastolic, hypotensive effect due to depression of central mechanisms of blood pressure regulation, inhibition of pressor reflexes, decrease in the allocation of catecholamines, aldosterone, decrease of vascular sensitivity to presorcents and direct vasodilating effect, prevents the loss of K +, exhibits antiarrhythmic action [9]. According to O.A. Thunder (2014), the state of acute and chronic stress is accompanied by catecholamine effects.

Under stress, an elevated amount of adrenaline and norepinephrine is released, which promotes the removal of magnesium from cells, decreases the intracellular content of magnesium, and high magnesium concentration in the primary urine and urinary losses [10]. According to literature, the use of magnesium medications improves the general state of hypertension, accompanied by regulatory disorders [11]. A special role in the treatment of magnesium deficient states belongs to the combined preparations containing magnesium and pyridoxine [12]. Correcting magnesium deficiency may improve endothelium dependent dilatation of the brachial artery [13].

Also, in the complex treatment of patients with hypertension, it is advisable to use drugs that have a tranquilizing effect, reduce the sense of anxiety. In clinical practice, the drug mebicer, which has moderate tranquilizing (anxiolytic) activity, relieves or weakens the feeling of anxiety, anxiety, fear, internal emotional stress and irritation, has a vegetative stabilizing effect [14].

Research purpose: to study the effects of the combination of pharmacotherapy with the preparation of magnesium and mebker on dynamics of indicators of cardiac hemodynamics and heart rate variability in patients with arterial hypertension stage II.

Materials and methods of research. A total of 145 patients with stage II AH, aged 29 to 53 years old (mean age 46.75 ± 0.56 years), were examined. Depending on the treatment received, the patients were divided into groups: Group I (n = 30) - patients receiving baseline therapy according to guidelines for AH [15]; Group II (n = 40) - patients who received on the background of basic therapy magnesium doses of 1 tablet. 3 p / day; Group III (n = 38) - patients received a Mebicar dose of 300 mg on the background of basic therapy. 3 p / day; Group IV (n = 37) - patients who received Mebicar in the background of baseline therapy at a dose of 300 mg 3 g / day and a magnesium drug in a dose of 1 tab. 3 p / day Duration of therapy - 1 month. The control group included 20 practically healthy people without hypertension, cardiovascular disease and overweight, comparable in age (mean age - 42.58 ± 1.45 years).

The diagnosis of AG was based on the provisions of the criteria of the Updated and Adapted Clinical Guideline, based on the evidence of Arterial Hypertension and the Unified Clinical Protocol for Primary, Emergency and Secondary (Specialized) Medical Aid "Arterial Hypertension" (Order of the Ministry of Health of Ukraine dated May 24, 2012, No. 384) [15].

All patients were given a standard general clinical and laboratory examination, electrocardiography, echocardiography (ultrasound scanner "Logic-5 XP" (GE, USA) 3.5 MHz sensor in the patient's position on the left side at an angle of 45 ° according to standard techniques).

Holter's round-the-clock ECG monitoring was carried out using the "Cardiolab" system manufactured by the company "KhAI-MEDICA" (Kharkiv, Ukraine). The following Cholter-ECG indices were evaluated: heart rate variability (HRC) in time and spectral measurements, which allowed to quantitatively characterize the activity of different parts of the autonomic nervous system. Time-based analysis is based on a study of changes in the duration of successive R-R intervals (heart rate) between sinus reductions. SDNN is the standard deviation from the mean duration of all sinus intervals R-R, which is an integral indicator characterizing the HRV as a whole and depends on the action of both the sympathetic and parasympathetic parts of the autonomic nervous system; RMSSD is the mean square difference between the duration of neighboring sinus intervals R-R; PNN 50% is the proportion of neighboring sinus intervals R-R, which differ by more than 50 ms. Spectral analysis of HBS was carried out on the basis of the analysis of the following indicators: HF (high frequency) - a high-frequency component of the spectrum (0.15-0.40 Hz); LF (low frequency) - low frequency component of the spectrum (0,04-0,15 Hz); LF / HF - simpato-parasympathetic balance; VLF (very low frequency) - very low frequency wavelength (0.0033-0.04 Hz); TP (total power) is the total power of the heart rate regulation spectrum.

They also conducted 24-hour daily monitoring of BP (DMBP) using the device AVRM-04 of the firm "Meditech" (Hungary). The average daily systolic and diastolic blood pressure (SBP and DBP, mm Hg), daily mean heart rate (heart rate, UDM / min) was analyzed [16].

Statistical processing of the received data. The statistical processing of the results of the study was conducted using the Statistica 10.0 software package (Stat Soft, Inc., USA). The significance of the differences between the groups was determined using Mann-Whitney's non-parametric criterion, as well as the Student's parametric criterion. Differences were considered significant at p <0.05.

Results of the study

Dynamics of average daily systolic, diastolic and pulse pressure (SBP, DBP, PBP) in patients with arterial hypertension was as follows (Table 1). SBP and GBP significantly decreased in patients with II and IV groups, with SBP in patients with these groups decreased by 25,8 (p <0,001) and 30,3% (p <0,01), and DBP - by 15,9 (p <0.001) and 12.5% (p <0.001), respectively. The expressed positive dynamics of PBP was also observed in patients II and IV groups - at 12, 5 and 12.0% (p <0.001; p <0.01). The impact volume increased in these patients, respectively, by 3.8% (p <0.05) and 4.8% (p <0.01). The ejection fraction increased by 6.3% (p <0.001) in patients with II group by 5.5% (p <0.01) - in patients of group IV.

An important indicator for assessing the therapeutic efficacy of the baseline and proven therapies is the heart rate variability (HRV). The analysis of HRV gives an opportunity to evaluate the effect of pharmacotherapy on the activity of the autonomic nervous system, and is also important for predicting the course of the disease.

In tabl. 2 shows the time and frequency analysis of the duration of intervals R-R - sinus rhythm. Indicators of time analysis correlate with each other. An unfavorable prognostic value is the decrease of HRV. At the same time, the increase of SDNNi, RMSSD, and PNN50% is a prognostic positive dynamics.

In patients of Group I (basic antihypertensive therapy) SDNNi is increased by 18.3% (p <0.01) in the daytime and by 20.0% at night (p <0.05). The most effective increase in SDNNi was observed in Group IV. In the afternoon, this increase was 45.8% (p <0.001), and at night, respectively, 73.3% (p <0.001). In general, the dynamics of RMSSD was the same as that of SDNNi, but was observed not only under the influence of simultaneous administration of magnesium and mebica (group IV), but also in II and III groups.

Table 1: Dynamics of clinical indexes for patients on by the hyperpiesis of the II stage under act of combined farmakoterapii by preparations of magnesium, mebicer and by preparations of magnesium in combination from mebicer (from data of additional methods of research)

Indexes	Norm n=20	I group n=30		II group n=40		III group n=38		IY group n=37	
		before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p
Systolic arterial pressure, millimeters of mercury pillar Δ%	125,90±1,22	161,78±0,57	145,57±0,63 Δ 16,2 *p*<0,001	167,86±1,23	142,00±1,01 Δ 25,8 *p*<0,001	163,24±0,92	145,20±1,08 Δ 18,0 *p*<0,001	172,83±0,74	142,52±0,93 Δ 30,3 *p*<0,001
diastolic arterial pressure, millimeters of mercury pillar,Δ%	80,70±1,18	104,30±0,58	95,52±0,31 Δ 8,8 *p*<0,001	107,86±0,44	91,95±0,68 Δ 15,9 *p*<0,001	105,32±0,47	93,16±0,38 Δ 12,2 *p*<0,001	106,35±0,27	93,87±0,36 Δ 12,5 *p*<0,001
pulsed arterial pressure, millimeters of mercury pillar, Δ%	63,00±2,04	75,83±1,89	69,13±1,75 Δ 6,7 *p*<0,05	91,95±2,43	79,41±2,29 Δ 12,5 *p*<0,001	81,04±2,42	71,60±2,40 Δ 9,4 *p*<0,01	88,91±2,93	77,04±2,40 Δ 12,0 *p*<0,01
echocardiography: shock volume, ml, Δ%	62,00±2,33	44,00±0,82	46,52±0,86 Δ 2,5 *p*<0,05	47,00±1,48	50,82±0,99 Δ 3,8 *p*<0,05	45,56±1,05	49,84±1,05 Δ 4,2 *p*<0,01	44,87±1,25	49,61±0,83 Δ 4,8 *p*<0,01
echocardiography Exit fraction, %, Δ%	56,20±0,39	51,39±0,85	54,57±1,14 Δ 3,2 *p*<0,05	48,36±0,49	54,68±0,44 Δ 6,3 *p*<0,001	49,80±1,10	54,56±1,05 Δ 4,8 *p*<0,003	51,04±1,50	56,52±1,26 Δ 5,5 *p*<0,01

Table 2: Influence of magnesium preparations, mebicer and preparations of magnesium in combination with mebacer on the dynamics of time analysis of round-the-clock Holter-ECG monitoring in patients with arterial hypertension of stage II

Indexes	Norm n=20	I group n=30		II group n=40		III group n=38		IY group n=37	
		before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p
SDNNi, мс^2 (in the day-time), Δ %	62,30±1,91	32,12±1,74	38,00±1,24 +Δ18,34 *p*<0,01	33,18±2,22	42,41±3,01 +Δ27,82 *p*<0,05	33,31±2,04	46,31±1,87 +Δ39,02 *p*<0,001	24,73±1,35	36,07±2,69 +Δ45,85 *p*<0,001
SDNNi, мс^2 (at night), Δ %	68,10±1,81	35,00±1,77	42,00±2,63 +Δ20,00 *p*<0,05	39,53±1,70	49,18±2,57 +Δ24,74 *p*<0,01	35,63±2,26	50,44±1,41 +Δ41,56 *p*<0,001	25,73±2,15	44,60±4,32 +Δ73,34 *p*<0,001
RMSSD, мс^2 (in the day-time),Δ %	24,90±0,90	10,76±0,32	13,29±0,59 +Δ23,51 *p*<0,001	9,94±0,41	14,47±1,35 +Δ45,57 *p*<0,01	8,44±0,52	13,94±1,61 +Δ65,16 *p*<0,01	13,67±0,79	20,60±0,94 +Δ50,69 *p*<0,001
RMSSD, мс^2 (at night), Δ %	27,80±1,39	12,82±0,32	15,18±0,92 +Δ18,41 *p*<0,05	11,29±0,25	17,06±1,77 +Δ51,11 *p*<0,01	10,94±0,30	17,31±1,92 +Δ58,3 *p*<0,01	15,07±0,90	22,20±0,68 +Δ47,31 *p*<0,001
PNN 50% (in the day-time),Δ %	8,36±0,24	1,31±0,17	2,18±0,21 +Δ66,41 *p*<0,01	2,35±0,46	5,77±0,50 +Δ145,5 *p*<0,001	2,77±0,48	5,54±0,69 +Δ200,0 *p*<0,01	2,78±0,48	5,09±0,52 +Δ83,09 *p*<0,01
PNN 50% (at night), Δ %	9,15±0,23	3,74±,39	5,00±0,38 +Δ33,69 *p*<0,05	3,95±0,53	6,95±0,53 +Δ75,95 *p*<0,001	4,46±,44	8,63±0,37 +Δ93,50 *p*<0,001	4,45±0,45	7,99±0,47 +Δ79,65 *p*<0,001

Table 3: Influence of magnesium, mebica and preparations of magnesium in combination with mebaker on the dynamics of HRF parameters (Holter-ECG monitoring) in patients with arterial hypertension of stage II

Indexes	Norm n=20	I group n=30		II group n=40		III group n=38		IY group n=37	
		before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p
LF, мс^2 (in the day-time), Δ %	303,50±50	153,71±14,15	216,47±15,52 +Δ40,8 *p*<0,01	173,18±31,07	288,41±31,77 +Δ66,5 *p*<0,05	110,75±8,82	255,63±31,04 +Δ130,8 *p*<0,001	111,13±17,45	238,73±41,50 +Δ114,8 *p*<0,01
LF, мс^2 (at night), Δ %	313,50±3,77	186,35±15,57	254,35±13,08 +Δ36,5 *p*<0,001	210,53±30,15	319,65±37,33 +Δ51,8 *p*<0,05	144,25±12,64	283,31±43,45 +Δ96,4 *p*<0,01	146,40±14,69	249,80±32,71 +Δ70,6 *p*<0,01
HF, мс^2 (in the day-time), Δ %	503,60±7,75	215,71±18,28	291,88±21,59 +Δ35,3 *p*<0,01	234,88±31,20	373,82±34,67 +Δ149,2 *p*<0,01	289,44±22,90	474,75±33,90 +Δ64,02 *p*<0,001	203,00±17,91	359,13±46,24 +Δ76,9 *p*<0,01
HF, мс^2 (at night), Δ %	514,9±9,22	293,29±24,76	399,59±29,99 +Δ36,2 *p*<0,01	300,59±30,87	438,65±36,05 +Δ45,9 *p*<0,01	351,00±20,35	505,06±57,98 +Δ43,9 *p*<0,05	256,07±17,16	403,40±46,96 +Δ57,5 *p*<0,01
LF/HF, (in the day-time), Δ %	1,52±0,79	2,25±0,10	1,70±0,07 -Δ24,4 *p*<0,001	3,32±0,20	2,50±0,11 -Δ24,7 *p*<0,002	3,19±0,14	1,98±0,07 -Δ37,9 *p*<0,001	3,38±0,20	2,21±,17 -Δ34,6 *p*<0,001
LF/HF, (at night), Δ %	1,32±0,05	2,14±0,03	1,89±0,04 -Δ7,5 *p*<0,015	3,38±0,25	2,74±0,14 -Δ18,9 *p*<0,05	2,46±0,08	1,43±0,06 -Δ41,87 *p*<0,001	3,32±0,24	2,41±0,19 -Δ27,4 *p*<0,01
VLF, мс^2 (in the day-time), Δ %	518,70±11,86	184,12±16,14	262,06±23,67 +Δ42,3 *p*<0,01	198,88±20,73	336,47±41,80 +Δ69,1 *p*<0,01	230,06±24,56	457,06±64,74 +Δ98,7 *p*<0,01	184,60±11,44	317,13±18,48 +Δ71,8 *p*<0,001
VLF, мс^2 (at night), Δ %	524,80±7,84	217,71±21,40	300,41±21,16 +Δ38,00 *p*<0,01	211,94±23,35	337,06±32,78 +Δ59,0 *p*<0,01	233,44±28,44	421,06±53,50 +Δ80,4 *p*<0,01	216,47±15,56	330,80±44,43 +Δ52,8 *p*<0,05
ТП, мс^2 (in the day-time), Δ %	1403,40±20,19	1035,65±32,94	1116,47±24,19 +Δ7,8 *p*<0,05	968,94±43,79	1173,53±51,29 +Δ21,0 *p*<0,01	1012,19±28,10	1217,06±57,58 +Δ20,2 *p*<0,01	1098,80±47,40	1315,33±31,74 +Δ19,7 *p*<0,001
ТП, мс^2 (at night), Δ %	1455,60±21,3	1107,76±23,44	1208,94±25,43 +Δ9,1 *p*<0,01	1094,94±48,11	1237,53±44,25 +Δ13,0 *p*<0,05	1099,13±24,03	1261,38±45,95 +Δ14,8 *p*<0,01	1132,93±23,62	1295,73±49,45 +Δ14,4 *p*<0,01

The dynamics of PNN 50% (day, night) was similar, which gives grounds for concluding about the activation of the parasympathetic nervous system (Table 2).

No less informative is the frequency analysis of the dynamics of the HSR. We included the LF (low frequencies - 0.04-0.15 Hz), HF (high frequencies - 0.15-0.40 Hz), VLF (very low frequencies - 0.0033-0.04 Hz), TP (full spectrum power), LF / HF (correlation of effects of sympathetic and parasympathetic nervous systems).

Low frequency heart rate fluctuations (LF, ms2) increased during treatment in all studied patients with hypertension. Moreover, this tendency did not depend on the daily rhythm. During the day, the increase in low frequency oscillations increased more than 2 times under the influence of a mebicar (110.75 ± 8.22 ms2 before treatment and 255.63 ± 31.04 ms2 after treatment, $p < 0.001$) and preparations of magnesium in combination with mebicar (111, 13 ± 17.45 ms2 before treatment and 238.73 ± 41.50 ms2 after treatment, $p < 0.01$). High-frequency oscillations of the heart rate also increased. Under the influence of a meal, an increase in HF in the afternoon was 64.02% ($p < 0.001$) compared with baseline. In the groups of magnesium preparations (II) and the combination of magnesium and mebicar drugs, an increase in HF was 149.2% ($p < 0.01$) and 76.90% ($p < 0.01$) (Table 3).

Reduction of hypersympathicotonia and its prevalence over parasympathetic manifestations was observed under the influence of a meicherum at 37.9% day. The night-time prevalence of sympathetic effects in the use of the meicherum decreased by 41.9% ($p < 0.001$). A similar tendency was preserved in patients with IV group (Table 3).

Conclusions

1. The main indicators of cardioghemodynamics in patients with arterial hypertension had the best positive dynamics when adding to the basic therapy of magnesium preparations and preparations of magnesium in combination with a mebicar, characterized by a steady decrease in the average daily values of systolic and diastolic blood pressure.
2. The investigated pharmaceutical products had a positive effect on the variability of the heart rate. In the process of treatment with magnesium and mebacar, the dynamic equilibrium between two autonomous systems was restored.

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