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THE EFFECTIVENESS OF LOW-DOSE RESERPINE-CONTAINING PHYTODRUGS IN THE TREATMENT OF ARTERIAL HYPERTENSION WITH METABOLIC SYNDROME IN YOUNG PATIENTS

Abstract. *The results of an open prospective clinical research on the use of low-dose reserpine-containing phytodrugs in young patients with mild hypertension and concomitant metabolic syndrome are presented. 56 young patients with arterial hypertension of 1st degree and concomitant metabolic syndrome with low and moderate cardiovascular risk were examined, the age was from 18 to 43 years old, male/female ratio was 32/24. Analyzing the results of the research, a significant antihypertensive effectiveness was revealed as in reducing of daily average blood pressure, and of day/night blood pressure. Effective blood pressure control (<130/80 mm Hg) was achieved in 75% patients. Additionally, the effect on carbohydrate and lipid metabolisms was assessed, and it was found the metabolic corrective action of low-dose reserpine-containing phytodrugs in young patients with mild hypertension and concomitant metabolic syndrome.*
Key words: arterial hypertension, metabolic syndrome, low-dose reserpine-containing phytodrug, antihypertensive effectiveness, metabolic correction.

Introduction. The problem of adequate blood pressure control in the population of patients with arterial hypertension remains unresolved around the world. In European countries, the proportion of patients who are treated effectively varies from 10 to 37%, in Ukraine among the urban population this indicator is 18.7% [1, 10].

One of the main reasons of inadequate blood pressure control is patient's low adherence to treatment, i.e. noncompliance with prescribed therapy regimen. Among the factors which adversely affect the patient's adherence to treatment are side effects of medicamentous therapy and patients' distrust of "chemical" drugs [3, 5].

The use of herbal extracts can be a supplement, and in some cases an alternative, for standard antihypertensive therapy. A large number of plants which decrease blood pressure are mentioned in various medicine manuals on herbal therapy, but almost there are no placebo-controlled researches that confirm this property. The exception is rauwolfia: its properties have been used for treatment for about 50 years [4, 5].

Rauwolfia and its alkaloid reserpine in the 50s of the twentieth century. became one of the first antihypertensive drugs that can effectively decrease blood pressure on taking per os and are suitable for long-term therapy of arterial hypertension. Due to the almost simultaneous appearance of rauwolfia, hydrochlorothiazide and hydralazine in those years, it became possible to effectively decrease blood pressure in patients with arterial hypertension and improve its prognosis [2, 4, 7].

These drugs were used to conduct the first prospective, placebo-controlled, randomized research "Veteran Administration Study (1967; 1970)", the results of which demonstrated the possibility of reducing mortality and complication rate in patients with arterial hypertension which received adequate antihypertensive therapy [8, 9].

The tablet of "Homviotensin" is a complex of four phytoextracts in low dilutions: Reserpine (D3 32 mg), Rauwolfia (D3 32 mg), Viscum album (mistletoe, D2 32 mg), Crataegus (hawthorn, D2 64 mg). There are several mechanisms of the antihypertensive effect of "Homviotensin". Firstly, sympatholytic action at the level of central and peripheral nervous system: depletion of reserves of nor-adrenaline in adrenergic nerve endings and a decrease in the content in the brain tissues of norepinephrine, dopamine, serotonin (reserpine, rauwolfia). Also there are vasodilating effect (slightly expressed in hawthorn due to improving

of endothelial function), influence on the vasomotor center of the medulla oblongata (mistletoe) and soft diuretic action (mistletoe, hawthorn). In addition, the drug exhibits mild sedative (rauwolfia, reserpine, hawthorn, mistletoe), antiarrhythmic (rauwolfia due to the alkaloid aymalin, hawthorn) and antioxidant (hawthorn) effects [2, 5].

A convincing evidence base which is based on the randomized double-blind research and 15 clinical trials testifies to antihypertensive efficacy of "Homviotensin" according to office blood pressure measurements and daily blood pressure monitoring. In the conducted researches, the antihypertensive effectiveness of "Homviotenzin" was shown, especially in mild arterial hypertension. The research structure did not include an assessment of the possible effect of low-dose reserpine-containing phytodrugs on the cocncomitant metabolic disorders of carbohydrate and lipid metabolism [7].

Objective: were to study the antihypertensive effectiveness of low-dose reserpine-containing phytoextracts in young patients with mild hypertension and concomitant metabolic syndrome and to assess their effect on the concomitant metabolic disorders of carbohydrate and lipid metabolism.

Materials and methods. 56 young patients with arterial hypertension of 1st degree (BP <160/100 mm Hg) and concomitant metabolic syndrome according to the criteria of IDF 2005, with modifications of 2009 (waist circumference ≥94 cm in men and ≥80 cm in women) with low and moderate cardiovascular risk were examined (ESC Guidelines 2013). The average age was 31.5 [18; 43] years old, male/female ratio was 32/24, average duration of AH was 2.2 [1.2; 5.4] years and average waist circumference was 101.2 [92.2; 114.4] cm (Table 1).

The complex low-dose reserpine-containing phytodrug "Homviotensin" (Homvoira Arzneimittel) was prescribed for patients on the background of lifestyle modification recommendations (DASH diet and dosed exercises). The drug was prescribed in dose 1 tablet 2 times a day (morning and evening), before 30 minutes or 30 minutes after meal, holding in the mouth until completely dissolution. If necessary (crises), the drug was taken additionally.

We studied the following secondary efficacy points: effective antihypertensive control according to daily blood pressure monitoring with registration of average heart rate indicators; indicators of lipid metabolism (total cholesterol, LDL, HDL, triglycerides); indicators of carbohydrate metabolism (fasting glucose, fasting insulin, HOMA index).

Table 1

Demographic and clinical data of examined patients, (M+m), (abs./%)

Indicator	N=56
Average age (years old)	31,5 [18;43]
M/F, abs.	32/24
Duration of AH (years)	2,2 [1.2; 5.4]
Systolic BP (mm Hg)	140,5 ± 4,6
Diastolic BP (mm Hg)	90,5 ± 2,8
Body mass index, kg/m^2	29,6±1,2
Waist circumference, cm	101,2 [92.2; 114.4]
Overweight (25>BMI<30), (abs./%)	12/21,4
Obesity (BMI>30), (abs./%)	40/71,4
Disorders of carbohydrate metabolism	
Fasting glycemia, (abs./%)	16/28,6
Insulinresistence (HOMA index >2,6), (abs./%)	26/46,4
Disorders of lipid metabolism	
Hypercholesterolemia, (abs. /%)	28/50
Hypertriglyceridemia, (abs. /%)	32/57,1
Decreased high density lipoproteins (HDL), (abs. /%)	22/39,3
Increased low density lipoproteins (LDL), (abs. /%)	30/53,6

The average duration of research was 60.2 ± 1.2 days.

Statistical processing of the obtained results was performed using the statistical processing software "Microsoft Excel 2003" and "Statistica 6.0". The arithmetic mean of the series (M), the mean error (m) were calculated. The probability of differences in average values between groups (independent samples), before and after treatment (dependent samples) was determined using Student's t-test, differences of indicators were significant when $p < 0,05$.

Results and discussion. Analyzing the dynamics of daily monitoring of blood pressure (Table 2) on the background of low-dose reserpine-containing phytodrugs in young patients with mild hypertension and concomitant metabolic syndrome, there was a significant decrease in the daily average SBP from (140,5 ± 4,6) to (128,2 ± 6,6) mm Hg ($p = 0,016$) and the daily average DBP from (90,5 ± 2,8) to (79,2 ± 2,6) mm Hg ($p=0,018$). There was also a significant decrease in daily SBP from (142,2 ± 3,6) to (130,4 ± 4,6) mm Hg ($p = 0,028$) and daily DBP from (92,9 ± 2,9) to (82,2 ± 2,6) mm Hg ($p = 0,024$). Indicators of night SBP and DBP also significantly decreased: from (134,4 ±

3,8) to (114,8 ± 2,2) mm Hg (p = 0,012) and from (84,4 ± 2,6) to (70,6 ± 2,2) mm Hg (p = 0,018), respectively. Also in examined patients on the background of treatment indicators of heart rate (HR) significantly decreased according to the daily monitoring: daily average, daytime, nighttime. Thus, the daily average heart rate decreased from (82,2 ± 3,6) to (68,2 ± 2,4) beats per minute (p < 0,001), daytime HR - from (88,3 ± 3,4) to (72,3 ± 3,2) beats/min. (p = 0,016), nighttime HR - from (78,1 ± 2,8) to (66,4 ± 2,6) beats/ min. (p = 0,014).

During studying the blood pressure profile according to daily monitoring data, the effective antihypertensive control (daily average BP less than 130/80 mm Hg) on the background of treatment was achieved in 42 (75%) examined patients. Thus, the use of low-dose reserpine-containing phytodrugs in young patients with mild hypertension and concomitant metabolic syndrome has a significantly expressed antihypertensive effectiveness, reduces daily average, daytime and nighttime BP.

Table 2

Antihypertensive effectiveness of low-dosed reserpine-containing phytodrugs according to daily blood pressure and heart rate monitoring, (M±m)

Indicator	N=56		
	Before treatment	After treatment	P
SBP daily average mm Hg	140,5 ± 4,6	128,2±6,6	0,016
DBP daily average mm Hg	90,5 ± 2,8	79,2±2,6	0,018
SBP day mm Hg	142,2±3,6	130,4±4,6	0,028
DBP day mm Hg	92,9±2,9	82,2±2,6	0,024
SBP night mm Hg	134,4±3,8	114,8±2,2	0,012
DBP night mm Hg	84,4±2,6	70,6±2,2	0,018
Heart rate, daily average, beats/min.	82,2±3,6	68,2±2,4	< 0,001
Heart rate, average/day, beats/min.	88,3±3,4	72,3±3,2	0,016
Heart rate, average/night, beats/min.	78,1±2,8	66,4±2,6	0,014

Note: SBP - systolic blood pressure, DBP – diastolic blood pressure,
p – significance of differences between results before and after treatment.

Estimating the effect of low-dose reserpine-containing phytodrugs in young patients with mild hypertension and concomitant metabolic syndrome on carbohydrate metabolism indicators (Table 3), it should be noted a significant decrease in the fasting blood glucose concentration in the examined patients from (5,8±0,5) to (5,1±0,3) mmol/l (p = 0,042), in the fasting insulin level decreased from (16,8 ± 0,31) to (12,6 ± 0,2) mcUn/ml (p = 0,041), in the HOMA index from (3,6±0,3) to (2,8±0,2) units (p=0,046). The significant decrease in the level of fasting glucose, insulin and HOMA index with usage of low-dose reserpine-containing phytodrugs indirectly indicates a decrease in insulinresistance and a positive effect of this phytotherapy on carbohydrate metabolism in young patients with mild arterial hypertension and concomitant metabolic syndrome.

Analyzing the dynamics of lipid metabolism in young patients with mild hypertension and concomitant metabolic syndrome with usage of low-dose reserpine-containing phytodrugs (Table 4), it should be noted a significant decrease in the total cholesterol from (5,4±0,3) to (5,0±0,2) mmol/l (p = 0,047). The level of triglycerides and

Table 3

Influence of low-dosed reserpine-containing phytodrugs on carbohydrate metabolism, (M±m)

Indicator	AH+MS (N=56)		
	Before treatment	After treatment	P
Fasting glucose, mmol/l	5,8±0,5	5,1 ± 0,3	0,042
Fasting insulin, mcUn/ml	16,8 ± 0,3	12,6 ± 0,2	0,041
HOMA index, units	3,6±0,3	2,8 ± 0,2	0,046

Note: p – significance of differences between results before and after treatment.

LDL also significantly decreased from (2,4±0,1) to (2,0±0,1) mmol/l (p = 0,045) and from (3,5±0,2) to (3,1±0,1) mmol/l (p = 0,041) respectively. The concentration of HDL significantly (p = 0,044) increased from (0,9±0,04) to (1,1±0,02) mmol/l. The revealed positive effect of low-dose reserpine-containing phytodrugs on lipid metabolism forms a favorable presupposition in

Table 4

Influence of low-dosed reserpine-containing phytodrugs on lipid metabolism, (M±m)

Indicator	AH+MS (N=56)		
	Before treatment	After treatment	P
Total cholesterol, mmol/l	5,4±0,3	5,0 ± 0,2	0,047
Triglycerides, mmol/l	2,4±0,1	2,0±0,1	0,045
HDL, mmol/l	0,9±0,04	1,1±0,02	0,044
LDL, mmol/l	3,5±0,2	3,1±0,1	0,041

Note: HDL - high density lipoproteins, LDL –low density lipoproteins,
p – significance of differences between results before and after treatment.

the prevention of atherosclerosis in young patients with mild hypertension and concomitant metabolic syndrome.

Conclusions. The use of low-dose reserpine-containing phytodrugs in young patients with mild arterial hypertension and concomitant metabolic syndrome has a significant antihypertensive effectiveness, which is manifested as a decrease of average daily, night blood pressure and heart rate.

Low-dose reserpine-containing phytodrugs may be effective as monotherapy in young patients with mild arterial hypertension and concomitant metabolic syndrome.

Low-dose reserpine-containing phytodrugs additionally have corrective effects on carbohydrate and lipid metabolism, which can make its use preferable in young patients with mild arterial hypertension and concomitant obesity or metabolic syndrome.

Prospects for further research. The revealed effectiveness of low-dose reserpine-containing antihypertensive therapy in young patients with arterial hypertension and metabolic syndrome and its associated metabolic corrective effects require further confirmation in more extensive researches. The proven effectiveness of this group of drugs forms a prospect for further pharmacological development and introduction of drugs with central sympatholytic action in guidelines on management of hypertension, especially in young patients with concomitant metabolic disorders.

References

1. Gorbas IM. Estimation of prevalence and control of arterial hypertension among the population of Ukraine. News of medicine and pharmacy. 2007; 229: 22-24 (in Russian).

2. Malaya LT, Koval SN, Snegurskaya IA. Clinical and hemodynamic efficacy of Homviotensin in patients with mild and moderate arterial hypertension. Phytotherapy. 2004; 2: 23-28 (in Russian).

3. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 350: 1903-1913.

4. Svishchenko EP, Mishchenko LA. Phytotherapy of hypertension from the standpoint of evidence-based medicine. Kiyv, Morion; 2009 (in Russian).

5. Svishchenko EP, Mishchenko LA. Homviotensin in the treatment of hypertensive patients. News of medicine and pharmacy. 2011; 15 (378): 10-14 (in Russian).

6. The results of clinical researches of "Homviotensin". Homvoira Arzneimittel. 2008: 9–126 (in Russian).

7. Turovskaya TV. The effectiveness of the Homviotensin in patients with mild and moderate arterial hypertension associated with the metabolic syndrome. Family medicine. 2010; 4: 101-106 (in Russian).

8. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of Treatment on Morbidity and Hypertension: Results in patients with diastolic pressures averaging 115 through 129 millimeters of mercury. JAMA. 1967; 202: 1028-1034.

9. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of Treatment on Morbidity and Hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 millimeters of mercury. JAMA. 1970; 213: 1143-1152.

10. Wolf-Maier K, Cooper RS, Kramer H et al. Hypertension treatment and control in five European countries, Canada and United States. Hypertension. 2004; 43: 7-10.