Pecularities of Prolonged Use of Moxonidine in Patients with Hypertension Associated with Metabolic Syndrome

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A 6-month clinical study with active therapeutic intervention was carried out to evaluate the efficacy of moxonidine for the correction of arterial hypertension in 30 patients with metabolic syndrome. Along with the metabolic neutrality for the lipid and purine metabolism, the drug demonstrated a distinct antihypertensive effect, which against the background of pronounced sympatholytic action after 3 months of therapy tends to disappear, which can be prevented by dosage correction. It was shown that the efficacy of moxonidine in reducing insulin resistance in patients with metabolic syndrome directly depends on the severity of hypersympathicotonia manifesting in heart rate over 80 bpm at rest.

Key Words: *hypertension; metabolic syndrome; carbohydrate metabolism; moxonidine*

The prevalence of metabolic syndrome (MS), a complex of factors determining high risk of cardiovascular morbidity and mortality, has reached a pandemic level in the beginning of the 21st century [2,5,9]. Undoubtedly, the correction of MS should begin with lifestyle changes. Unfortunately, patients able to overcome entrenched patterns of behavior, *i.e.* change dietary habits, increase physical activity, and break of bad habits are a rare exception from the total number of individuals suffering from this disease [1,9]. In such a situation, pharmacotherapy had moved to the forefront. Normalization of blood pressure (BP), being a top priority in the treatment of these patients, allows to halve the number of major cardiovascular complications [1,8,12]. In this case, hypotensive drugs should be at least metabolically neutral and the treatment should be pathogenetically justified, which helps to reduce problems associated with polypragmasy [10,12].

In recent decades, the leading role of the hyperactive sympathetic system in the genesis of metabolic disorders was clearly proven [4,7,13]. In this context, of particular importance in the therapy of patients with MS is the use of sympatholytic antihypertensive drugs with central action, *e.g.* selective I_1 imidazoline receptor agonists, in particular, of moxonidine, the most widely presented preparation in domestic market [3,11,13]. However, it should be noted that published data on the effect of moxonidine on carbohydrate and lipid metabolism in these patients are controversial [3,11,13,14].

Here we studied antihypertensive, sympatholytic activity and pleiotropic effects of moxonidine therapy in patients with arterial hypertension (AH) associated with MS.

MATERIAL AND METHODS

Thirty patients with MS receiving antihypertensive therapy (13 males and 17 females, mean age 49.70± 3.16 years, mean history of AH 5.17±0.73 years) were followed-up for 6 months. The study was carried out in accordance with the Helsinki Declaration. Written informed consent was obtained from all the patients participating in the study. Inclusion criterion was consistency addressing the recommendations of the International Diabetes Federation in 2005 for

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verification of MS [15]. The patients were examined before treatment, after 3 weeks and 3 and 6 months of moxonidine therapy for evaluation of antihypertensive, sympatholytic, and metabolic effects of the drug. Antihypertensive effect was studied according to international recommendations by daily ambulatory BP monitoring (ABPM) using an ABPM-04 Meditech system. Sympatholytic effect of the drug was estimated by plasma concentration of the main neuroendocrine axis hormones, ACTH and cortisol (by ELISA). To estimate the parameters of carbohydrate metabolism in fasting state and 2 h after standard breakfast, serum concentration of glucose (at endpoint) and insulin (ELISA) was examined. Insulin resistance was diagnosed by HOMA-R index (Homeostasis Model Assesment), calculated by the formula: fasting insulin level (μU)×fasting glucose (mmol/liter)/22.5. Parameters of lipid metabolism in blood serum were determined by enzymatic colorimetric method. Purine metabolism was characterized by the concentration of uric acid using the enzymatic (urikase) method.

After primary examination, all patients received moxonidine, a selective imidazoline receptor agonist (Physiotens – Solvay Pharma) in a starting dose of 0.2 mg once daily after breakfast. If the hypotensive effect was not satisfactory 3 weeks and 3 months after the start of treatment, the dose was increased to 0.4 mg/day according to the same scheme. If a dose >0.4 mg was required, it was divided into two intakes. The maximum dose used was 0.6 mg/day.

Quantitative data were expressed as mean±standard error of the mean ($M\pm m$). The data were processed using nonparametric Wilcoxon rank test and Mann–Whitney U test. For all statistical tests, the differences were significant at $p<0.05$. For comparison of qualitative variables, Fisher's angular transformation was used. The correlations between quantitative variables were assessed by correlation coefficient (R).

RESULTS

No cases of side effects requiring drug withdrawal were recorded, which indicates its good tolerability and safety. As a result of therapy, the clinical condition of patients improved. The patients reported a decrease of dyspnea and improvement of working capacity and exercise tolerance as soon as after 3-week treatment, while after 6 months of therapy, the percent of patients without complaints increased from 0 to 61.1% ($p<0.05$).

During the study, the level of BP by the results of BP monitoring was first of all assessed in patients treated with moxonidine in terms specified by the protocol. After 3 weeks of treatment, a statistically

TABLE 1. Dynamics of 24-h BP and HR Parameters during Moxonidine Therapy ($M\pm m$)

Parameter	Before treatment	Duration of treatment		
		3 weeks	3 months	6 months
SBP 24 h, mm Hg	149.33±4.38	133.67±4.33*	144.33±2.19^{+}	133.17±2.05*^{o}
DBP 24 h, mm Hg	94.08±2.68	79.83±2.44*	90.89±2.52	79.00±1.99*^{o}
SBP daytime, mm Hg	153.83±4.55	138.83±4.52*	146.33±1.50^{+}	137.58±2.12*^{o}
DBP daytime, mm Hg	96.75±3.15	84.75±2.72*	89.78±2.76	83.83±2.42*^{o}
PTI SBP daytime, %	76.67±5.61	54.92±6.93*	76.78±3.91^{+}	56.50±4.74*^{o}
PTI DBP daytime, %	68.17±8.85	53.25±8.45	64.33±9.87	43.58±7.00*
SBP nighttime, mm Hg	146.25±4.33	123.25±3.84*	131.25±4.18	124.42±2.97*
DBP nighttime, mm Hg	87.33±2.58	70.33±1.99*	73.62±2.43	72.17±2.98
PTI SBP nighttime, %	78.92±6.03	45.75±9.02*	73.88±8.31^{+}	57.50±8.67
PTI DBP nighttime, %	57.58±9.32	45.58±7.30	54.25±12.50	54.83±9.20
DI SBP, %	8.55±1.82	11.00±1.52	11.58±1.94	12.08±1.66
DI DBP, %	17.50±2.46	16.50±2.42	16.25±1.94	14.83±3.38
Average daytime HR, bpm	76.00±2.88	77.42±4.38	78.75±3.89	77.25±3.19
Average nighttime HR, bpm	65.83±2.36	66.33±4.24	66.75±3.34	66.83±2.90

Note. DBP, diastolic BP; SBP, systolic BP; PTI, pressure-time index, DI, index of daily mean blood pressure. Here and in Table. 2, 3: $p<0.05$ compared to: *baseline values, $^{+}$3 weeks, ^{o}3 months.

TABLE 2. Cortisol and ACTH Concentrations in Patients with AH and MS during Moxonidine Therapy (*M*±*m*)

Parameter	Moxonidine therapy (*N*=30)	Before treatment		
		3 weeks	3 months	6 months
Cortisol, nmol /liter	638.57±85.12	577.15±73.50	644.30±93.70	578.97±47.16
ACTH, pg/ml	43.52±6.92	37.46±5.36	30.66±4.19	27.76±3.09*

significant reduction in the daytime, nighttime, and 24-h systolic and diastolic BP was revealed ($p<0.05$). However, after 3 months of moxonidine treatment, a significant increase was observed in 24-h and daytime levels of systolic BP measured at BP monitoring compared to the levels observed after 3 weeks of therapy. The dynamics of diastolic BP was the same (Table 1). This required increasing the dose of the drug in 61.1% patients. After 6 months, moxonidine after dosage adjustment significantly reduced the 24-h systolic and diastolic BP to the target values. A statistically significant reduction in daytime and nighttime BP levels and pressure-time index of systolic and diastolic BP was also recorded. Moxonidine did not interfere with normal circadian oscillation of BP. On the basis of the dynamics of circadian BP parameters at monitoring, a stable, uniform reduction in BP within a day was found. The target level of BP was achieved in 72.2% patients.

Evaluation of sympatholytic activity of the drug by the dynamics of the ACTH and cortisol concentrations revealed initial hypersympathicotonia in 16-20% patients. During 6-month antihypertensive therapy, the level of ACTH gradually decreased and by the end of the observation period was below the initial level by 36.21% ($p<0.05$). At the same time, blood cortisol concentration after an initial decrease by 9.6% ($p>0.05$) increased by 10.43% to the 3rd month of therapy ($p>0.05$) compared to the level observed after 3 weeks and did not differ from baseline (Table 2). After 6 months of moxonidine therapy, the cortisol levels decreased by 9.3% from the baseline and by 10.1% compared with the period of 3 months ($p>0.05$). Direct relationship between the dynamics of cortisol levels and the degree of daily systolic and diastolic BP reduction in patients receiving moxonidine treatment ($R=0.9$ for systolic and $R=0.95$ for diastolic; Fig. 1) was noted.

Thus, moxonidine therapy significantly decreased plasma ACTH levels in patients with MS, which is related to the direct sympathetic blocking action of moxonidine and attests to a significant inhibition of the central compartment of the sympathetic nervous system. The absence of significant changes in cortisol content is apparently associated with its great variability within the normal range and high sensitivity of the organism to various factors. The observed dynamics of cortisol concentration can be associated with attenuation of therapeutic effect of moxonidine determined by the receptor mechanism of its action due to inhibition of catecholamine release from adrenal chromaffin cells.

No marked dynamics of fasting blood glucose level was detected (Table 3), while basal insulin concentration tended to decrease by 22.8% ($p>0.05$). The decrease in basal insulin levels was manifested in a decrease in HOMA-R insulin resistance index. Although insulin resistance was initially diagnosed in 100% patients and the incidence of its detection did not change at different stages of treatment, HOMA-R index decreased by an average of 18.74% ($p>0.05$) by the end of therapy. This fact can be explained by a direct effect of the drug on I_1-imidazoline receptors of the pancreas, which ensures optimal physiological insulin secretion in response to glucose load. It was demonstrated that in patients with baseline levels of cortisol above the average level, moxonidine therapy decreased more markedly the index of insulin resistance than in all patients of this group: by 32% ($p>0.05$; Fig. 2). At the same time, in patients with baseline levels of cortisol

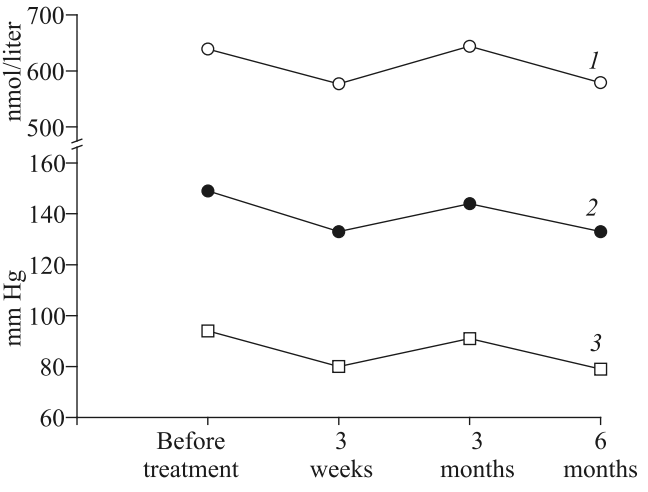

Fig. 1. Dynamics of cortisol levels and diurnal systolic (SBP) and diastolic BP (DBP) in patients with AH and MS. *1*) cortisol; *2*) SBP 24 h; *3*) DBP 24 h.

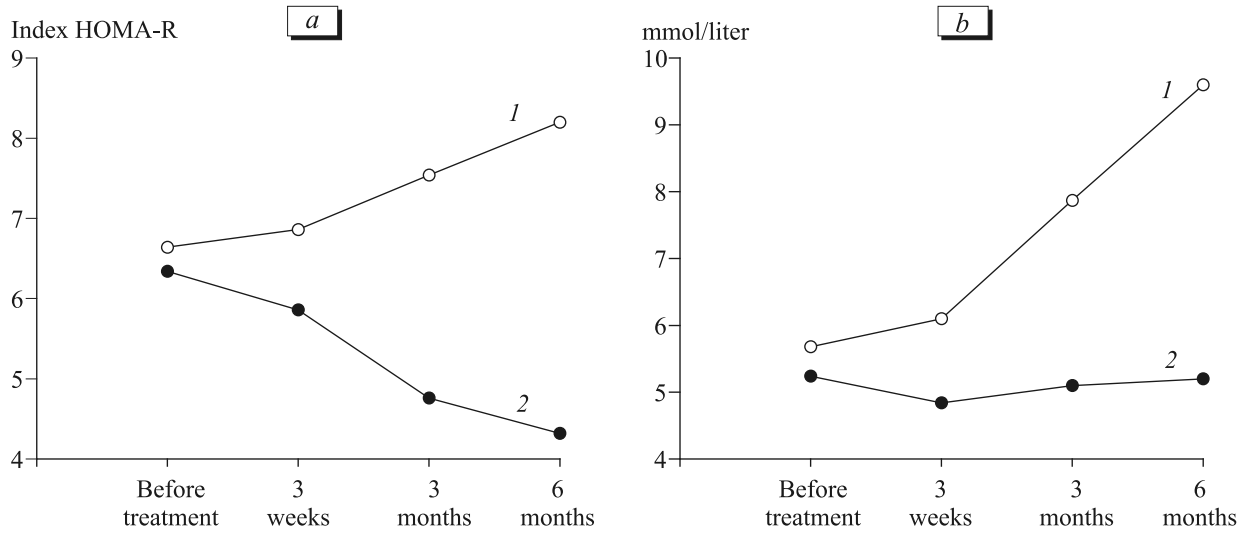

Fig. 2. Dynamics of insulin resistance index HOMA-R (*a*) and postprandial blood glucose (*b*) in patients with AH and MS depending on the initial cortisolemia during moxonidine therapy. *1*) patients with initially high levels of cortisol; *2*) patients with cortisol levels below the group mean.

below the average group level, insulin resistance index increased by 14.6% compared with baseline value ($p>0.05$). Consequently, the efficiency of correction of insulin resistance with moxonidine depends on the severity of hypersympathicotonia.

In the absence of appreciable dynamics of postprandial insulinemia in patients treated with moxonidine, the postprandial glucose concentration after 6 months of treatment increased by 16.5% ($p<0.05$) compared to baseline level. At the same time, the postprandial glucose levels negatively correlated with cortisol concentration. In patients with initial hormone concentration below average group values, postprandial glucose concentration increased by on average 57.7% during the therapy (Fig. 2).

The direct relationship between HR and the level of cortisolemia should be emphasized. Daytime HR in the group was 76.00±2.88 bpm, whereas in patients with initially high blood cortisol level HR was 87.12±4.38 bpm.

TABLE 3. Parameters of Metabolism during Moxonidine Therapy (*M*±*m*)

Parameter	Moxonidine (*N*=30)	Before treatment		
		3 weeks of treatment	3 months of treatment	6 months of treatment
Fasting plasma glucose, mmol/liter	5.72±0.22	5.56±0.19	5.69±0.25	5.78±0.24
Fasting insulin, μU/ml	25.23±5.46	22.78±5.78	20.15±2.88	19.48±2.83
HOMA-R index	6.51±1.48	5.54±1.48	5.37±0.99	5.29±0.91
Postprandial glucose levels, mmol/liter	5.77±0.41	5.50±0.47	6.19±0.68	6.91±0.58*
Postprandial insulin levels, μU/ml	44.59±7.29	46.18±11.17	56.60±9.75	59.03±11.00
Total cholesterol, mmol/liter	5.66±0.23	5.63±0.16	5.64±0.21	5.67±0.21
LDL, mmol/liter	3.32±0.49	3.31±0.40	3.31±0.59	3.22±0.26
VLDL, mmol/liter	0.92±0.19	0.94±0.18	0.91±0.20	0.88±0.13
HDL, mmol/liter	1.42±0.23	1.38±0.17	1.42±0.28	1.57±0.31
Triglycerides, mmol/liter	2.05±0.21	2.16±0.42	2.11±0.37	1.99±0.35
Atherogenic index	3.43±0.36	3.29±0.38	3.21±0.43	3.13±0.39
Uric acid, μmol/liter	360.38±26.60	330.54±25.05	356.85±23.77	369.08±30.24

No significant changes in parameters of lipid metabolism were revealed throughout the treatment period (Table 3). However, positive dynamics of the index of atherogenicity, the index reflecting predisposition for atherosclerosis development and its progression, was detected after 6 months of treatment: before moxonidine treatment it was elevated in 53.3% patients, while after 6 months only in 30% ($p>0.05$). No appreciable changes in the dynamics of purine metabolism parameters were revealed (Table 3).

The effectiveness of the drug in the correction of insulin resistance directly depends on the severity of hypersympathicotonia. Imidazoline receptor agonists are not indicated for patients with HR at rest <80 bpm because of possible worsening of carbohydrate metabolism disorders. Moxonidine had positive effects on glucose metabolism and insulin resistance in patients with high activity of the sympathetic nervous system (HR at rest >80 bpm). Due to pronounced hypotensive effect, moxonidine can be recommended as a drug of choice for these patients. However, the observed attenuation of therapeutic effect after 3 months of treatment agrees with current views on peculiar pharmacodynamics of drugs acting at the level of receptors [6]. At the same time, timely dose correction makes it possible to achieve target BP thus probably reducing the incidence of cardiovascular complications and mortality and improving the prognosis.

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