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The use of telmisartan in the treatment of arterial hypertension with obesity

The combined course of arterial hypertension (AH) with overweight or abdominal obesity is considered as one of the most common type of comorbid pathology leading to a significant increase of cardiovascular complications.

Aim. To study the effects of telmisartan on the intracardiac hemodynamics, the functional state of the myocardium, the lipid and carbohydrate profile in patients with arterial hypertension (AH) and obesity.

Materials and methods. 50 patients with AH of stage II were examined, they were divided into 2 groups. The first (main) group consisted of 23 patients with stage II arterial hypertension and the normal body weight. In the second group (reference group) there were 27 patients, who were diagnosed with AH of stage II and obesity. The diagnosis was verified using laboratory instrumental methods in accordance with the recommendations of the European Cardiologic Society (2013). Obesity was assessed by the body mass index and the waist to the hip ratio. The lipid profile was determined by the enzymatic method.

Results. It has been found in the study that the level of values of systolic blood pressure (SBP) in hypertensive patients with the normal body weight treated with telmisartan decreased by 14.5 %, while diastolic blood pressure (DBP) reduced by 11.4 %. In patients with AH of stage II having obesity the SBP level also decreased by 13.4 % and DBP – by 11.5 %. In 3 months of treatment the regression dynamics of the end-diastolic and end-systolic dimensions of the heart in the group of patients without obesity led to a significant decrease in these parameters compared to the baseline values. In obese patients these indicators also decreased; however, they did not reach reliable values. When treating with telmisartan there was a decrease in lipids in AH patients (total cholesterol (TC)– (5.5 %), cholesterol of low density lipoproteins (LDL) – 6.2 %, triglycerides (TG) 7.8 %, cholesterol of HDL – by 10.4 % ($p < 0.05$), there were also unreliable changes in AH patients associated with obesity (total cholesterol – by 5.9 %, LDL – 5.1 %, TG – 8.8 % and increased cholesterol of HDL – by 6.4 %). After the treatment the indicators of carbohydrate metabolism decreased (glycosylated hemoglobin (HbA1c) by 8.45 % and 19.17 %, insulin – by 3.2 % and 13.38 % glucose – by 5.65 % and 4.73 %, respectively, in groups).

Conclusions. The study has shown that telmisartan has indirect positive effects on intracardiac hemodynamics due to decrease of blood pressure both in AH patients having the normal body weight and patients with obesity. The use of telmisartan as an antihypertensive agent gives a hypolipidemic effect, improves the parameters of the carbohydrate metabolism in AH patients with the normal body weight and with obesity. These data can be markers for assessing the effectiveness of hypotensive therapy with telmisartan.

Key words: arterial hypertension; obesity; hemodynamics; lipids; telmisartan

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Застосування телмісартану в лікуванні артеріальної гіпертензії з ожирінням

Поєднаний перебіг артеріальної гіпертензії (АГ) з надлишковою масою тіла або з абдомінальним ожирінням розглядаються як один з найбільш розповсюджених варіантів коморбідної патології, що приводить до значного підвищення частоти серцево-судинних ускладнень.

Метою роботи було вивчення ефектів телмісартану на внутрішньосерцеву гемодинаміку, функціональний стан міокарда, ліпідний і вуглеводний профіль у хворих на артеріальну гіпертензію з нормальною масою тіла і артеріальною гіпертензією (АГ) з ожирінням.

Матеріали та методи. Обстежено 50 хворих на АГ II стадії, які були розподілені на 2 групи. Першу (основну групу), склали 23 пацієнти з артеріальною гіпертензією II ступеня і з нормальною масою тіла. Другу групу (порівняння) склали 27 пацієнтів, у яких діагностувалась АГ II ст. з ожирінням. Діагноз верифікували з використанням лабораторно-інструментальних методів. Ожиріння оцінювали по індексу маси тіла і співвідношенню об'єму талії до об'єму стегон. Визначення ліпідного профіля проведене ферментативним методом.

Результати. Результати свідчать, що рівень «офісних» значень систолічного артеріального тиску (САТ) у хворих на АГ з нормальною масою тіла при вживанні телмісартану знижувався на 14,5 %, а діастолічного – на 11,4 %. У хворих на АГ II ст. з ожирінням рівень САТ також знижувався на 13,4 % і діастолічного – на 11,5 %. Через 3 місяці лікування динаміка регресу кінцево-діастолічного і кінцево-систолічного розміру серця у групі пацієнтів без ожиріння приводила до достовірного зменшення цих показників у порівнянні з початковими значеннями. У хворих з ожирінням ці показники також зменшувались, проте не досягали достовірних значень. При лікуванні із застосовуванням телмісартану відбувалось зниження ліпідів у хворих на АГ (загальний холестерин (ХС) – на 5,5 %, ХС ліпопротеїдів низької щільності (ЛПНЩ) – на 6,2 %, тригліцеридів (ТГ) – на 7,8 % і підвищення ХС ЛПВЩ – на 10,4 % ($p < 0,05$) та недостовірні зміни у хворих на АГ з ожирінням (ЗХС – на 5,9 %, ХС ЛПНЩ – на 5,1, ТГ – на 8,8 % і підвищення ХС ЛПВЩ – на 6,4 %). Після проведеного лікування ці показники зменшувались (глікозильованого гемоглобіну (HbA1c) на 8,45 % і на 19,17 %, інсуліну – на 3,2 % і на 13,38 %, глюкози – на 5,65 % і на 4,73 % відповідно по групах).

Висновки. Телмісартан опосередковано позитивно впливає на внутрішньосерцеву гемодинаміку за рахунок зниження артеріального тиску як у хворих на артеріальну гіпертензію з нормальною масою тіла, так і з ожирінням. Застосування телмісартану як гіпотензивного заходу дає гіполіпідемічний ефект і покращує показники вуглеводного обміну у хворих на артеріальну гіпертензію як з нормальною масою тіла, так і з ожирінням. Наведені дані можуть бути орієнтирами для оцінки ефективності проведення гіпотензивної терапії телмісартаном.

Ключові слова: артеріальна гіпертензія; ожиріння; гемодинаміка; ліпіди; телмісартан

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Применение телмисартана в лечении артериальной гипертензии с ожирением

Сочетанное течение артериальной гипертензии (АГ) с избыточной массой тела или абдоминальным ожирением рассматриваются как один из наиболее распространенных вариантов коморбидной патологии, приводящее к значительному повышению частоты сердечно-сосудистых осложнений.

Целью работы было изучение эффектов телмисартана на внутрисердечную гемодинамику, функциональное состояние миокарда, липидный и углеводный профиль у больных артериальной гипертензией с нормальной массой тела и артериальной гипертензией (АГ) с ожирением.

Материалы и методы. Обследовано 50 больных АГ II стадии, которые были разделены на 2 группы. Первую (основную группу) составили 23 пациента с артериальной гипертензией II степени с нормальной массой тела. Вторую группу (сравнения) составили 27 пациентов, у которых диагностировалась АГ II ст. с ожирением. Диагноз верифицировали с использованием лабораторно-инструментальных методов. Ожирение оценивали по индексу массы тела и соотношению объема талии к объему бедер. Определение липидного профиля проведено ферментативным методом.

Результаты. Исследованием установлено, что уровень значений систолического артериального давления (САД) у больных АГ с нормальной массой тела при употреблении телмисартана снижался на 14,5 %, а диастолического – на 11,4 %. У больных АГ II ст. с ожирением уровень САД также снижался на 13,4 % и диастолического – на 11,5 %. Через 3 месяца лечения динамика регресса конечно-диастолического и конечно-систолического размеров сердца в группе пациентов без ожирения приводила к достоверному уменьшению этих показателей по сравнению с исходными значениями. У больных с ожирением эти показатели также уменьшались, однако не достигали достоверных значений. При лечении с применением телмисартана происходило снижение липидов у больных АГ (общий холестерин (ХС) – на 5,5 %, ХС липопротеидов низкой плотности (ЛПНП) – на 6,2 %, триглицеридов (ТГ) – на 7,8 % и повышение ХС ЛПВП – на 10,4 % ($p < 0,05$) и недостоверные изменения у больных АГ с ожирением (ОХС – на 5,9 %, ХС ЛПНП – на 5,1 %, ТГ – на 8,8 % и повышение ХС ЛПВП – на 6,4 %). После проведенного лечения показатели углеводного обмена уменьшались (гликозилированного гемоглобина (HbA1c) на 8,45 % и 19,17 %, инсулина – на 3,2 % и 13,38 %, глюкозы – на 5,65 % и 4,73 % соответственно по группам).

Выводы. Телмисартан косвенно положительно влияет на внутрисердечную гемодинамику за счет снижения артериального давления как у больных артериальной гипертензией с нормальной массой тела, так и с ожирением. Применение телмисартана в качестве гипотензивного средства дает гиполипидемический эффект и улучшает показатели углеводного обмена у больных артериальной гипертензией как с нормальной массой тела, так и с ожирением. Приведенные данные могут быть ориентирами для оценки эффективности проведения гипотензивной терапии телмисартаном.

Ключевые слова: артериальная гипертензия; ожирение; гемодинамика; липиды; телмисартан

Currently, arterial hypertension (AH) in combination with overweight or with abdominal obesity is considered as one of the most common type of comorbid pathology leading to a significant increase of cardiovascular complications [1].

In recent years, the adipose tissue is considered not only as a depot of lipids, but also as a tissue that has auto-, para- and endocrine properties. Adipocytes are a dynamic tissue and always vary, depending on the genetic and nutritional status of the body [2]. Adipogenesis wedges into the physiological and pathological conditions that need therapeutic correction.

Preadipocytes are formed from the multipotent embryonic stem cells of the mesodermal origin, and then they are converted into adipocytes, chondrocytes, osteoblasts or monocytes. Only preadipocytes suspended in growth under the action of C / EBP1, ADD1 / SREBP1 proteins can turn into mature adipocytes. Sterol proteins that bind regulatory elements (SREBP – sterol regulatory element-binding proteins) and are known as transcriptional modulators of many numerous genes; they are involved in the metabolism of cholesterol and fatty acids and in protein coding. Expression of the factors induced by C/EBPβ and C/EBP regulates the expression of PPARY2 [3]. Immature adipocytes, as a result of transcriptional events, begin to accumulate lipid droplets and hypogeneous and lipolytic enzymes. In addition, mature adipocytes decree highly specific and too late differentiation markers, such as leptin, adiponectin, resistin, visfatin, omentin, adipsin, and others. These molecules not only regulate the metabolism of lipoproteins and glucose, but also have pro- (leptin and resistin) and anti-inflammatory (adiponectin) properties [4].

PPARY binds and activates many of the genes that capture and store fatty acids. In numerous experiments its role in the transformation of adipocytes has been revealed in both *in vitro* gene expression

and *in vivo* target genes in mice, indicating an important role of PPARY in adipogenesis. Therefore, PPARY is the main pharmacological target of adipogenesis.

The aim of our work was to study the effects of telmisartan on the intracardiac hemodynamics, the functional state of the myocardium, the lipid and carbohydrate profile in patients with AH and obesity.

Materials and methods

Fifty AH patients with the normal body weight (NBW) and with obesity included in the study, and they were divided into 2 groups. The first (main group) consisted of 23 patients with AH of stage II and NBW. In the second group (reference group) there were 27 patients, who were diagnosed with AH of stage II and obesity. Telmisartan was administered in the dose of 40 mg once a day. The average age of the patients under study was 62.7 ± 6.4 years (from 45 to 74 years old); men were 42 % and women – 58 %. The mean values of systolic blood pressure (SBP) in the patients were 166.2 ± 5.6 mm Hg, while the mean diastolic blood pressure (DBP) was 97.3 ± 2.6 mm Hg. The heart rate (HR) was 86.7 ± 2.4 beats per min. Chronic heart failure was not higher than AH of stage II. The study also included 20 people without signs of hypertension, diabetes and obesity (the heart rate was within normal limits) as a control group (their average age was 52.4 years, from 40 to 59 years old, there were 12 men, and 8 women). Groups were comparable by gender, age, severity of clinical condition, concomitant pathology.

The criteria for inclusion of patients in the study were the presence of the clinical signs of hypertension confirmed by the data of additional methods of examination. Clinical diagnosis was established on the basis of the patient's complaints, anamnesis of the disease, and data of physical examination. The diagnosis was verified using laboratory instrumental methods in accordance with the recommendations of the European Cardiologic Society (2013). The following instrumental methods were used: electrocardiography in 12 standard leads in prone position after 5 minutes of rest; transthoracic echocardiography (Philips HD11XE, USA, according to the generally accepted Echo-pulse method with the ultrasound frequency of 7.5 MHz).

TheeExclusion criteria were as follows: patients with concomitant acute inflammatory, infectious, oncologic, immune and rheumatologic diseases, AH patients with the ejection fraction <50 %, anemia, renal insufficiency, acute heart failure episodes, acute coronary syndrome within the previous 3 months, disturbances of rhythm, and conduction, chronic obstructive pulmonary diseases, occlusive diseases of the vessels of the lower extremities.

The body weight was assessed by the body mass index (BMI) recommended by the WHO. The optimal BMI was considered within the range of 18.5-24.9 kg/m^2. The criterion for overweight was BMI of 25-29.9 kg/m^2, and for obesity – more than 30.0 kg/m^2. The anthropometric indicator for obesity of stage I was 30.6 ± 1.4 kg/m^2. In addition to the body weight and height, the waist to hip ratio was taken into account; the visceral type of distribution of the fatty tissue was determined: in women with the waist-to-hip ratio it was more than 0.85; in men – > 1.0 [5].

The biochemical studies of lipids included determination of total cholesterol (TC), triglycerides (TG) and cholesterol of high-density lipoproteins (HDL) in the plasma by the enzymatic method using DIAKON-DS sets (Russia).

The content of cholesterol of LDL was calculated according to the formula: cholesterol of LDL (mmol/L) = TC: 2.2. The level of cholesterol of HDL was calculated by the difference between TC and the remaining lipoprotein fractions. The atherogenic index (AI) was calculated according to the formula: AI = (TC – cholesterol of HDL): cholesterol of HDL. The normal limits were selected by the criteria most often used in clinical and epidemiological studies [6].

The work was carried out in accordance with the requirements of the Helsinki Declaration of the World Medical Association, the Charter of Ukrainian Association of Bioethics and standards GCP (1992), in accordance with the requirements and standards of ICH GCP (2002) pursuant to the provisions on ethics of the Ministry of Health of Ukraine No. 66 dated 13.02.2006. All patients expressed their informed consent for participation in the study and were fully aware of the methods and scope of the study.

Since the quantitative variables in all compared groups were close to the normal probability distribution, parametric methods were used. The critical value of the significance level p was 0.05. Qualitative and quantitative indicators were assessed using absolute and relative (percentage) frequencies. The central pattern and variability of quantitative indicators were calculated by bringing the arithmetic mean value (M) and standard deviation (m); the results were presented in the form of: M ± m. The statistical hypothesis concerning the absence of difference between two comparable groups was tested using suitable Student's test (for dependent or independent samples). Mathematical calculations were carried out in SOFA Statistics.

Results and discussion

The analysis of 3-month treatment with angiotensin II receptor inhibitor telmisartan showed that the level of values of systolic blood pressure (SBP) (Tab.) in AH patients with NBW decreased by 14.5 % ($p < 0.05$), while diastolic blood pressure reduced by 11.4 % ($p < 0.05$). In patients with AH of stage II

Table

The changes in the cardiac hemodynamic, lipid and carbohydrate metabolism in hypertensive patients with the normal body weight and with obesity when treating with telmisartan

Indicators	Control group (n = 20)	AH with the normal body weight (n = 23)		AH with obesity (n = 27)	
		before treatment	after treatment	before treatment	after treatment
Systolic BP	121.5±4.3	154.8±5.6	132.3±4.5*	163.7±5.8	141.7±4.6*
Diastolic BP	75.6±2.4	95.3±3.7	84.4±2.7	98.6±3.6	87.3±3.1*
ESD, cm	3.8±0.02	4.38±0.12#	4.17±0.08*	4.43±0.13	4.19±1.1
EDD, cm	5.0±0.02	5.44±0.11#	5.19±0.12*	5.67±0.12	5.45±.11
ESV, ml	62.3±1.5	84.17±2.3	77.4±3.5*	92.54±3.1	86.4±3.6
EDV, ml	132.4±2.3	168.76±5.6	157.4±5.3*	184.48±6.2	171.6±6.3
TLVPW, cm	0.98±0.02	1.46±0.03	1.41±0.02*	1.48±0.03	1.43±0.02
IST, cm	0.91±0.02	1.47±0.03	1.39±0.02*	1.49±0.04	1.42±0.03
EF, %	65.7±1.7	60.3±0.9	62.2±1.3	59.7±0.8	61.5 ±1.1
LA, cm	3.6±0.2	4.32±0.3	4.1±0.2	4.4±0.3	4.2±0.2
TC, mmol/L	4.61±0.07	5.69±0.17	5.38±0.12*	5.93±0.21	5.58±0.16
Cholesterol of LDL, mmol/L	2.78±0.07	4.06±0.13	3.81±0.11*	4.33±0.19	4.11±0.14
Cholesterol of HDL, mmol/L	1.51±0.04	0.96±0.02	1.06±0.03*	0.78±0.02	0.83±0.03
TG, mmol/L;	1.68±0.06	2.04±0.08	1.88±0.09	2.17±0.13	1.98±0.07
HbA1c, %	4.57±0.51	5.04±0.49	4.62±0.48	5.94±0.53	4.76±0.47
Insulin, μU/ml	7.94±0.43	8.73±0.29	8.45±0.24	9.87±0.36	8.55±0.23
Glucose, mmol/l	4.49±0.11	4.78±0.13	4.51±0.11	5.29±0.12	5.04±0.09

Notes:
1) # – $p < 0.05$ compared to the control group;
2) * – $p < 0.05$ compared to the group of patients before treatment.

having obesity the SBP level also decreased by 13.4 % ($p < 0.05$), and DBP – by 11.5 % ($p < 0.05$). When assessing the effects of telmisartan on the level of blood pressure depending on the type of remodeling of the lungs a significant antihypertensive effect was observed in all variants of the lung geometry.

In patients with AH of stage II with NBW and with concomitant obesity the larger sizes of the left ventricular cavity were observed: left ventricular end-systolic dimension (LVESD) and left ventricular end-diastolic dimension (LVEDD) ($p < 0.05$). In 3 months of treatment the regression dynamics of the LVEDD (by 4.6 %) and LVESD (by 4.8 %) of the heart in the group of patients without obesity led to a significant decrease in these parameters compared to the baseline values ($p < 0.05$). In obese patients these indicators also decreased; however, they did not reach reliable values. This indicates a significant decrease in the ventricular preload and ventricular afterload during treatment with telmisartan.

The left ventricular wall thickness reduction was observed in patients without obesity, which remained reliable in compared to the group with obesity. Changes in the myocardial walls among all patients from clinical groups occurred mainly due to a decrease in the interventricular septum thickness (IST) by 5.5 % and to a lesser extent – the thickness of the left ventricular posterior wall in diastole (TLVPW) by 3.4 % under the action of treatment. In obese patients the decrease in these indicators was not reliable. This may indicate that in patients with obesity the pathological process is more pronounced and the antihypertensive therapy in these patients does not lead to a significant change in the processes of fibrous remodeling of the myocardium.

Positive changes were presented by improvement of the functional state of the myocardium and the left atrium offload when treating with telmisartan. Therefore, in patients from both groups (AH with NBW and with obesity) the left ventricular ejection fraction increased by 3.15 % and by 3.01 %, and the diameter of the left atrium decreased by 5.1 % and by 4.5 %, respectively. The similar changes occurred with the end-systolic and end-diastolic volume.

The analysis of the lipid plasma spectrum of the blood in AH patients with NBM and with obesity showed a significant increased level of TC by 23.4 %

($p < 0.05$), TG – by 21.4 % ($p < 0.05$), cholesterol of LDL – by 46.04 % and decrease in cholesterol of HDL by 36.4 % compared to the control group. The similar changes were noted in the group of AH with obesity. TC increased by 28.6 % ($p < 0.05$), cholesterol of LDL – by 55.7 % ($p < 0.05$), TG by 29.2 % ($p < 0.05$), while cholesterol of HDL decreased by 51.6 % ($p < 0.05$) compared to the control group. These changes indicate a decrease in the cholesterol-acceptor properties of cholesterol of HDL, which manifests itself by their acidification modification and accumulation of cholesterol in cell membranes.

There were no significant differences between the indicators of the lipid blood spectrum in both AH groups with and without obesity, but there was a tendency for increasing atherogenic lipoproteins and decreasing antiatherogenic lipoproteins. These changes are due to the active process of transferring cholesterol esters from HDL to LDL in exchange for TG under conditions of hypertriglyceridemia.

When treating with telmisartan there was a decrease in lipids in AH patients with NBW: TC – by 5.5 % ($p < 0.05$), cholesterol of LDL – by 6.2 % ($p < 0.05$), TG – by 7.8 % ($p > 0.1$) and an increase in cholesterol of HDL – by 10.4 % ($p <0.05$), there were also unreliable changes in AH patients associated with obesity: TC – by 5.9 % ($p > 0.1$), cholesterol of LDL – by 5.1 % ($p > 0.1$), TG – by 8.8 % ($p > 0.1$), and increased cholesterol of HDL – by 6.4 % ($p > 0.1$). Such data underline that, possibly, telmisartan increased the effect of hypolipidemic agents more in AH patients with NBM and less in AH patients with obesity.

Indicators of carbohydrate metabolism were increased compared to the control before treatment (glycosylated hemoglobin (HbA1c) – by 10.28 % and 29.98 %, insulin by – 9.95 % and 24.3 %, glucose – by 0.5 % and 17.8 %, respectively). After the treatment these indicators decreased (HbA1c – by 8.45 % and 19.17 %, insulin – by 3.2 % and 13.38 % glucose – by 5.65 % and 4.73 %, respectively, in groups).

Currently, there are three independent classes of targets in adipocytes that are suitable for therapeutic interventions in obesity and diabetes: adipokines, modulators of hormonal sensitivity and enzymes involved in preservation of lipids. The second class has already been approved as the main target for PPARY agonists, a class of antidiabetic drugs (thiazolidinediones) that increase insulin sensitivity. However, these drugs have side effects in the form of the weight gain, edema and heart failure [7].

The angiotensin II receptors blockers of the first type (sartans) can neutralize the effect of PPARY activation on the weight gain and, in parallel, maintain a positive metabolic effect. At the same time, the sensitivity of the tissue to insulin increases. Sartanes also selectively block receptors ATR1, and it leads to stimulation of angiotensin II receptors of the second type (ATR2 and PPARY) [8]. The stimulation of these receptors is accompanied with hypolipidemic effects of sartans (TC, TG, LDL, and high-density lipoproteinemia). Furthermore, they reduce the content of free fatty acids and increase the expression of adiponectin, which increases the tissue sensitivity to insulin. Telmisartan reduces the adipocyte size in rats with the fructose diet and increases glucose tolerance [9].

The study of telmisartan effects on the functional state of the myocardium and intracardiac hemodynamics, the lipid and carbohydrate metabolism shows its high efficacy. This is probably due to a decrease in the left ventricular hypertrophy, and improvement of the elastic properties of the myocardium as a result of the indirect effect through reducing blood pressure and the effect of cholesterol, TG on the metabolism. The results obtained can be taken into account when assessing the effectiveness of telmisartan in AH treatment.

CONCLUSIONS

1. Telmisartan has an indirect positive impact on intracardiac hemodynamics by reducing blood pressure in AH patients with NBW and with obesity.

2. The use of telmisartan as an antihypertensive agent gives a hypolipidemic effect in AH patients with NBW and with obesity.

3. When treating with telmisartan there is normalization of the carbohydrate metabolism (glycosylated hemoglobin, glucose and insulin).

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