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Relationship between cardiac rhythm disorders, serum urotensin II and angiotensin II levels in patients with stage II hypertension and carotid atherosclerosis in dynamics of treatment with candesartan and lercanidipine

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Key words: Hypertension, Arrhythmias, Urotensin II, Angiotensin II, Candesartan, Lercanidipine.

Arterial hypertension is one of the most common diseases of the cardiovascular system.

Aim – to study dynamics of cardiac rhythm disorders, serum urotensin II and angiotensin II levels in patients with stage II hypertension associated with carotid atherosclerosis during treatment with candesartan and lercanidipine.

Methods of the study. Under our observation there were 122 patients with stage 2 hypertension aged between 36–75 years. Average age of the patients was 51.52 ± 1.27 years, including men – 52 (43 %), women – 70 (57 %). Cardiac arrhythmias and conduction disorders were detected by means of Holter ECG. Serum urotensin II and angiotensin II levels in the blood serum were determined by use of an immunoenzymatic method. Statistical analysis was performed by means of the Statistica® 6.0 for Windows (StatSoft Inc.) software using parametric and nonparametric methods.

Results. It was found that the receiving of lercanidipine and candesartan showed unidirectional positive effect on cardiac rhythm disorders in most patients with stage II hypertension. The use of candesartan statistically insignificantly increased levels of angiotensin II in patients of the first group of observation by 20.8 % compared with baseline values ($p > 0.05$). However, as a result of candesartan treatment serum angiotensin II levels in patients with stage II hypertension without carotid atherosclerosis reliably increased by 47.1 % ($p < 0.05$). Unlike candesartan, the use of lercanidipine leads to a statistically significant decrease in the concentration of urotensin II by 30.8 % ($p < 0.05$) in patients with stage II hypertension associated with carotid atherosclerosis.

Conclusions. Lercanidipine can be recommended as a first line antihypertensive drug in case of simultaneous hypertension and atherosclerotic lesion of brachiocephalic arteries.

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Взаємозв'язок між порушеннями серцевого ритму, сироватковим рівнем уротензину II та ангіотензину II в пацієнтів із гіпертонічною хворобою II стадії, що асоційована з каротидним атеросклерозом, у динаміці лікування кандесартаном і лерканідипіном

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Артеріальна гіпертензія є одним із найпоширеніших захворювань серцево-судинної системи.

Мета роботи – вивчити динаміку порушень серцевого ритму, сироваткового рівня уротензину II та ангіотензину II в пацієнтів із гіпертонічною хворобою II стадії, що асоційована з каротидним атеросклерозом, у процесі лікування кандесартаном і лерканідипіном.

Матеріали та методи. Під нашим спостереженням перебували 122 пацієнти (52 (43 %) чоловіки та 70 (57 %) жінок) із гіпертонічною хворобою II стадії віком 36–75 років. Середній вік хворих – $51,52 \pm 1,27$ року. Порушення серцевого ритму та провідності виявляли шляхом здійснення холтерівського моніторингу ЕКГ. Визначення концентрації уротензину II та ангіотензину II в сироватці крові здійснювали за допомогою імуноферментного методу шляхом вимірювання оптичної щільності зразків, що досліджували. Статистичне опрацювання результатів виконали з використанням програми «Statistica® 6.0 for Windows» (StatSoft Inc.) із застосуванням параметричних і непараметричних методів.

Результати. Встановили, що приймання лерканідипіну та кандесартану продемонструвало односпрямований позитивний вплив на динаміку порушень серцевого ритму в більшості пацієнтів із гіпертонічною хворобою II стадії. Застосування кандесартану призводило до статистично не значущого зростання рівня ангіотензину II в пацієнтів першої групи спостереження на 20,8 % ($p > 0,05$) порівняно з вихідними даними. Водночас приймання кандесартану у хворих із гіпертонічною хворобою II стадії без атеросклеротичного ураження брахіоцефальних артерій вірогідно підвищувало концентрацію ангіотензину II на 47,1 % ($p < 0,05$). На відміну від кандесартану використання лерканідипіну призводило до статистично значущого зниження сироваткового рівня уротензину II на 30,8 % ($p < 0,05$) у хворих із гіпертонічною хворобою II стадії, що асоційована з атеросклеротичним ураженням сонних артерій.

Висновки. Лерканідипін може бути рекомендований як препарат першої лінії в умовах поєднаного перебігу артеріальної гіпертензії та атеросклеротичного ураження брахіоцефальних артерій.

Ключові слова: гіпертензія, аритмії, уротензин II, ангіотензин II, кандесартан, лерканідипін.

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Взаимосвязь между нарушениями сердечного ритма, сывороточным уровнем уротензина II и ангиотензина II у пациентов с гипертонической болезнью II стадии, ассоциированной с каротидным атеросклерозом, в динамике лечения кандесартаном и лерканидипином

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Артериальная гипертензия является одним из наиболее распространённых заболеваний сердечно-сосудистой системы.

Цель работы – изучить динамику нарушений сердечного ритма, сывороточного уровня уротензина II и ангиотензина II у пациентов с гипертонической болезнью II стадии, ассоциированной с каротидным атеросклерозом, в процессе лечения кандесартаном и лерканидипином.

Материалы и методы. Под нашим наблюдением находились 122 пациента (52 (43 %) мужчины и 70 (57 %) женщины) с гипертонической болезнью II стадии в возрасте 36–75 лет. Средний возраст больных составил $51,52 \pm 1,27$ года. Нарушения сердечного ритма



и проводимости выявлялись путём проведения холтеровского мониторирования ЭКГ. Определение концентрации уротензина II и ангиотензина II в сыворотке крови осуществляли с помощью иммуноферментного метода путём измерения оптической плотности исследуемых образцов. Статистическая обработка полученных результатов проводилась с использованием программы «Statistica® 6.0 for Windows» (StatSoft Inc.) с применением параметрических и непараметрических методов.

Результаты. Установлено, что приём лерканидипина и кандесартана оказывал однонаправленное положительное влияние на динамику нарушений сердечного ритма у большинства пациентов с гипертонической болезнью II стадии. Применение кандесартана приводило к статистически не значимому росту уровня ангиотензина II у пациентов первой группы наблюдения на 20,8 % ($p > 0,05$) по сравнению с исходными значениями. В то же время приём кандесартана у больных с гипертонической болезнью II стадии без атеросклероза сонных артерий достоверно повышал концентрацию ангиотензина II на 47,1 % ($p < 0,05$). В отличие от кандесартана, использование лерканидипина приводило к статистически значимому снижению сывороточного уровня уротензина II на 30,8 % ($p < 0,05$) у больных с гипертонической болезнью II стадии, ассоциированной с атеросклеротическим поражением сонных артерий.

Выводы. Лерканидипин может быть рекомендован в качестве препарата первой линии в условиях сочетанного течения артериальной гипертензии и атеросклеротического поражения брахиоцефальных артерий.

Ключевые слова: гипертензия, аритмии, уротензин II, ангиотензин II, кандесартан, лерканидипин.

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Arterial hypertension (AH) is one of the most common diseases of the cardiovascular system. Uncontrolled hypertension is associated with high risk of cardiovascular, cerebrovascular and renal complications [1]. Large-scale meta-analysis did not establish significant advantages of the one group of first-line drugs over another regarding ability to lower blood pressure (BP), and the current national and European guidelines indicate the necessity to evaluate the initial cardiovascular risk and patient's comorbidities when choosing antihypertensive therapy [2].

According to current clinical guidelines on hypertension, angiotensin II receptor blockers (ARBs) are a group of drugs that are often prescribed by the doctor for treatment of AH. High adherence to the medication is associated with its safety, practically absent side effects, simplicity of administration (1 per day), stable antihypertensive effect, organ protective properties [3].

One of the medications that reduce BP most effectively is a calcium antagonist lercanidipine. Its advantages are high lipophilicity, vasoselectivity, membrane-controlled pharmacokinetics and one of the best in the class tolerability profiles [4].

It was demonstrated that in general the treatment with lercanidipine did not reveal any effect on heart rate. The number of patients with ventricular and/or supraventricular arrhythmias also did not changed significantly after 2 weeks of therapy with lercanidipine [5].

For the first time, the LIFE study demonstrated reduction in relative risk of atrial fibrillation (AF) during treatment of hypertensive patients with losartan 67 % compared to atenolol [6]. At present, this effect is confirmed for other ARBs (candesartan, valsartan, irbesartan). J. Healey et al. 2005 in a meta-analysis which included 11 trials (56308 patients) reported a decrease in AF risk by 28 %, including among patients with AH – 12 %. Possible mechanisms for this effect are clinical hemodynamic unloading of the heart, reduction of remodelling and direct antiarrhythmic effect.

It was found that dihydropyridine calcium channel blockers have different effects on the level of angiotensin II (AT II) in the blood serum. Thus, Konda T. et al. demonstrated increased AT II level during treatment with amlodipine [7].

At the same time, lercanidipine reduced the level of peptide by expanding both afferent and efferent renal arterioles [8].

Zheng Z. et al. established that ARBs increases the level of AT II in the blood due to hyperactivation of renin-angioten-

sin-aldosterone system [9]. In addition, under the influence of azilsartan the level of AT II and plasma renin activity increases and aldosterone concentration decreases [10].

Certain changes occur with the level of urotensin II (UT II) in blood during treatment with ARBs and calcium channel blockers. Thus, the concentration of UT II reduced due to losartan [11]. Nicardipine intake also led to a decrease in the concentration of peptide [12].

Today there is a lack of evidence from international randomized multicentre research study of antiarrhythmic effect of lercanidipine and candesartan, and their ability to reduce the risk of cardiovascular complications in patients with hypertension combined with carotid atherosclerosis. It is relevant to study the effect of these drugs on serum levels of AT II and UT II in patients with stage II hypertension (HTN), associated with the pathology of extracranial arteries.

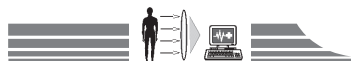
Objective

To study dynamics of cardiac rhythm disorders, serum urotensin II and angiotensin II levels in patients with stage II hypertension combined with carotid atherosclerosis during treatment with candesartan and lercanidipine.

Methods of the study

Under our observation there were 122 patients with stage 2 HTN aged between 36–75 years. Average age of the patients was 51.52 ± 1.27 years, including men – 52 (43 %), women – 70 (57 %). Patients with stage 2 HTN were divided into two groups according to the results of Doppler ultrasound of the great arteries of the head. Patients with HTN associated with carotid atherosclerosis, who had the average value of intima media thickness of the common carotid artery 1.4 mm or more, comprised the first group of observation. Patients with stage 2 HTN were included in the second group of observation. Both groups were comparable by gender, age, stage and duration of HTN. The control group consisted of 30 relatively healthy individuals.

Inclusion criteria were the presence of stage 2 HTN, age over 18 years, written voluntary consent for participation in this study. Exclusion criteria were as follows: the history of stroke or brain hemorrhage, coronary artery disease, congestive heart failure (III, IV functional class by NYHA), cardiomyopathy, congenital and acquired heart disease, peptic and duodenal ulcer, dysfunction of the thyroid gland.



Depending on the applied therapy patients of the first group of observation were randomized in the two groups of 30 patients each. 31 patients of the second clinical group received candesartan, other 31 persons – lercanidipine. Subgroups of patients were actually compared on grounds such as average age, sex, duration of hypertension medical history, levels of office blood pressure and heart rate. If there was no decrease in blood pressure at least by 10 % compared with baseline values after the first week of treatment, the protocol supposed to add to treatment indapamide 1.5 mg per day. The course of treatment was 12 weeks.

Cardiac arrhythmias and conduction disorders were detected by means of Holter ECG. During the period of study patients followed the usual daily regimen. The duration of monitoring was 24 hours. During observation, patients kept so-called patient’s diary in order to compare the registered ECG record and patient’s action at this point.

Serum UT II and AT II levels were determined in the Central Research Laboratory of Zaporizhzhya State Medical University using ELISA microplate reader SIRIO S (Italy) and reagents produced by Peninsula Laboratories (USA); this process was based on the measurement of optical density of the samples according to the manufacturer’s instructions. 84 serum samples of patients with HTN were studied, including the period of treatment. All values were obtained automatically and calculated in ng/ml.

Statistical analysis was performed by means of the Statistica® 6.0 for Windows (StatSoft Inc.) software using parametric and nonparametric methods. In case of normal distribution of the studied variables data are presented as average and standard deviation (SD) and as median. For all types of analysis differences are considered statistically significant when $p < 0.05$.

In case of non-normal distribution U-Mann-Whitney test was applied for two independent samples, Wilcoxon test for comparing two dependent samples and Kruskal-Wallis criterion followed by Games-Howell comparison test for more samples.

To analyse the effect of treatment on the studied values in case of normal data distribution the univariate repeated measures ANOVA followed by Newman-Keuls or Games-Howell tests were used, given the multiplicity of comparisons. In cases when the distribution of the studied variables did not meet the assumption of normality, the Friedman test was used as a non-parametric analogue to the repeated measures ANOVA. Comparisons of two groups were performed using Wilcoxon test.

Results and discussion

Analysis of the data demonstrated that treatment with candesartan resulted in positive changes regarding cardiac rhythm disorders in patients with arterial hypertension (*Table 1*). Thus, the patients of the first group of observation showed statistically significant reduction in the number of supraventricular arrhythmias and the difference was 13.0 % ($p < 0.05$).

As for paired ventricular extrasystoles in patients with stage II HTN and carotid atherosclerosis observed differences were not reliable, compared with the baseline values 21.2 % ($p > 0.05$). In the first clinical group treatment with candesartan resulted in no significant decrease in both isolated premature ventricular contractions – 9.7 % ($p > 0.05$) and polymorphic ventricular extrasystoles – 28.8 % ($p > 0.05$). Thus, after treatment for supraventricular and isolated ventricular extrasystoles differences between individuals in the control group and patients with stage II HTN and carotid atherosclerosis kept statistically significant.

In the second clinical group during therapy with candesartan patients experienced a significant reduction in the number of both supraventricular premature complexes – 18.2 ($p < 0.05$) and paired ventricular extrasystoles – by 59.4 % ($p < 0.05$). As for other types of arrhythmia the following dynamics was established in patients with stage II HTN without carotid atherosclerosis: isolated ventricular extrasystoles reliably decreased by 14.8 % ($p > 0.05$) and polymorphic ventricular premature contractions – by 16.8 % ($p > 0.05$).

Candesartan administration in patients of the first group observation led to the decrease in the number of patients with AF to 2 persons, although before the treatment their number was 3. As a result of antihypertensive therapy there were no patients with AF among the patients diagnosed for stage II HTN without carotid atherosclerosis.

Both groups of observation demonstrated positive dynamics under the influence of lercanidipine treatment in therapy of cardiac rhythm disorders (*Table 2*). Thus, patients with stage II HTN and carotid atherosclerosis showed no significant decrease in the number of supraventricular arrhythmias and the difference was 12.6 % ($p > 0.05$). At the same time, 12-week treatment with lercanidipine demonstrated a statistically significant difference regarding isolated ventricular extrasystoles – 15.6 % ($p < 0.05$) as well as polymorphic ventricular premature contractions – 56.1 % ($p < 0.05$). In addition, patients of the first clinical group had no reliable reduction in paired ventricular beats – 18.6 % ($p > 0.05$). Differences between individuals in the control group and pa-

Table 1

Dynamics of cardiac arrhythmias in hypertensive patients during treatment with candesartan

Types of arrhythmia	Control group (n=7)	Patients with arterial hypertension and carotid atherosclerosis (n=18)		Patients with stage II hypertension (n=10)	
		Before treatment	After treatment	Before treatment	After treatment
Supraventricular arrhythmias	102.45±18.8	320.97±12.3*	279.33±14.2* ¹	278.25±12.4*	207.51±11.2* ¹
Isolated ventricular extrasystoles	34.71±10.2	218.14±12.5*	196.89±13.7*	187.34±12.4*	159.67±13.1*
Polymorphic ventricular extrasystoles	–	36.43±10.4*	25.93±11.3*	28.64±10.2*	23.83±10.1*
Paired ventricular extrasystoles	–	24.02±3.2*	18.93±4.1*	14.31±2.9*	5.81±3.1* ¹

Notes: * – indicates significant difference from the corresponding values of the control group ($p < 0.001$); ¹ – indicates significant difference from baseline values ($p < 0.05$).



tients with stage II HTN and carotid atherosclerosis remained statistically significant after treatment for both supraventricular arrhythmias and isolated ventricular extrasystoles.

Among the patients of the second clinical group 12-week treatment with lercanidipine did not lead to any significant changes in the types of arrhythmia. However, some positive dynamics was observed in patients with stage II HTN without carotid atherosclerosis: supraventricular arrhythmias statistically insignificantly decreased by 9.8 % ($p>0.05$), isolated ventricular extrasystoles – by 10.7 % ($p>0.05$), polymorphic ventricular premature contractions – 21.6 % ($p>0.05$) and paired ventricular extrasystoles – by 19.3 % ($p>0.05$).

In addition, as for 3 patients in the first group of observation who had paroxysms of AF before treatment with lercanidipine, by the end of treatment this type of arrhythmia remained only in 1 patient. The number of patients with stage II HTN without carotid atherosclerosis and AF didn't changed as a result of treatment and was 2 persons.

Analysis of the data (Table 3) allowed to affirm that during treatment with candesartan serum levels of UT II in patients with

hypertension associated with carotid atherosclerosis tended to decrease compared with the rate before treatment – by 21.4 % ($p>0.05$). As a result of treatment serum levels of AT II in patients of the first group of observation statistically insignificantly increased by 20.8 % compared with baseline values ($p>0.05$). In patients with stage II HTN and carotid atherosclerosis significant differences between the final levels of UT II, AT II and those of the control group remained.

Patients of the second group of observation showed no statistically significant difference in the UT II levels before and after treatment with candesartan – 24.0 % ($p>0.05$). However, as a result of treatment serum AT II levels in patients with stage II HTN without carotid atherosclerosis reliably increased by 47.1 % ($p<0.05$). It should be noted that among the second group of observation differences from the control group regarding serum UT II, AT II levels kept statistically significant.

12-week treatment with lercanidipine had a positive effect on serum UT II and AT II concentrations in patients with arterial hypertension (Table 4). Thus, among the first group of observation as a result of treatment serum UT II levels statistically

Table 2

Dynamics of cardiac arrhythmias in hypertensive patients during treatment with lercanidipine

Types of arrhythmia	Control group (n=7)	Patients with arterial hypertension and carotid atherosclerosis (n=19)		Patients with stage II hypertension (n=9)	
		Before treatment	After treatment	Before treatment	After treatment
Supraventricular arrhythmias	102.45±18.8	320.18±14.8*	279.71±13.9*	273.21±13.7*	246.54±13.2*
Isolated ventricular extrasystoles	34.71±10.2	224.89±12.1*	189.74±12.5**	186.62±12.2*	166.72±11.8*
Polymorphic ventricular extrasystoles	–	38.93±8.1*	17.11±7.2**	27.42±7.5*	21.49±7.2*
Paired ventricular extrasystoles	–	22.71±3.2*	18.49±3.7*	11.34±2.9*	9.15±2.4*

Notes: * – indicates significant difference from the corresponding values of the control group ($p<0.001$); # – indicates significant difference from baseline values ($p<0.05$).

Table 3

Dynamics of serum UT II and AT II levels in hypertensive patients during treatment with candesartan

Parameter	Control group (n=8)	Patients with arterial hypertension and carotid atherosclerosis (n=20)		Patients with stage II hypertension (n=22)	
		Before treatment	After treatment	Before treatment	After treatment
UT II, ng/ml	0.08±0.02	0.42±0.05*	0.33±0.04*	0.25±0.03*	0.19±0.03#
AT II, ng/ml	0.06±0.01	0.24±0.03*	0.29±0.04*	0.17±0.02*	0.25±0.03* ¹

Notes: * – indicates significant difference from the corresponding values of the control group ($p<0.001$); # – indicates significant difference from the corresponding values of the control group ($p<0.05$); ¹ – indicates significant difference from baseline values ($p<0.05$).

Table 4

Dynamics of serum UT II and AT II levels in hypertensive patients during treatment with lercanidipine

Parameter	Control group (n=8)	Patients with arterial hypertension and carotid atherosclerosis (n=20)		Patients with stage II hypertension (n=23)	
		Before treatment	After treatment	Before treatment	After treatment
UT II, ng/ml	0.08±0.02	0.39±0.05*	0.27±0.04* ¹	0.23±0.03*	0.17±0.03#
AT II, ng/ml	0.06±0.01	0.23±0.04*	0.18±0.03*	0.15±0.02*	0.10±0.02

Notes: * – indicates significant difference from the corresponding values of the control group ($p<0.001$); # – indicates significant difference from the corresponding values of the control group ($p<0.05$); ¹ – indicates significant difference from baseline values ($p<0.05$).



significantly decreased compared with baseline values – by 30.8 % ($p < 0.05$). At the same time, serum AT II concentrations statistically insignificantly dropped during treatment with lercanidipine in this group of patients – by 21.7 % ($p > 0.05$). Differences between patients with stage II HTN and carotid atherosclerosis with those in the control group regarding both serum UT II and AT II levels remained reliable.

Patients of the second group of observation receiving lercanidipine for 12 weeks did not result in a reliable decrease of serum UT II and AT II concentrations. Thus, serum UT II decreased only by 26.1 % ($p > 0.05$) and AT II – by 33.3 % ($p > 0.05$).

In addition, AT II after treatment was not statistically significantly different from the control group as opposed to UT II regarding which differences remained statistically significant.

Conclusions

1. The use of lercanidipine and candesartan in most patients with stage II hypertension showed unidirectional positive effect on cardiac rhythm disorders.

2. Treatment with candesartan resulted in increased angiotensin II level in patients in both observation groups.

3. Unlike candesartan, the use of lercanidipine leads to a statistically significant urotensin II concentration decrease by 30.8 % ($p < 0.05$) in patients with stage II hypertension associated with carotid atherosclerosis, and can be recommend as the first antihypertensive line in this category of patients.

Conflicts of Interest: authors have no conflict of interest to declare.

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