

УДК 616.12-008.331.1-085

DOI: <https://doi.org/10.17816/PAVLOVJ119880>

Терапевтический лекарственный мониторинг при неконтролируемой артериальной гипертензии: результаты пилотной части исследования

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АННОТАЦИЯ

Введение. Несмотря на сложившийся в последние годы доказательный и системный подход к лечению артериальной гипертензии (АГ) далеко не во всех случаях удается достичь ее контроля.

Цель. Провести сравнительный анализ концентрации антигипертензивных препаратов (АГП) в сыворотке крови пациентов с контролируемой и неконтролируемой АГ.

Материалы и методы. Включено 56 пациентов. Критерии включения: возраст ≥ 18 лет, подписание информированного согласия, установленный диагноз АГ, регулярный прием в течение месяца двух любых изучаемых (лизиноприл, амлодипин, валсартан) АГП, а также индапамида в стабильных дозах, для женщин — адекватная контрацепция. По результатам суточного мониторирования артериального давления (АД) пациенты были распределены на две группы: первая — контролируемая АГ (АД $< 140/90$ мм рт. ст.; $n = 39$), вторая — неконтролируемая АГ (АД $\geq 140/90$ мм рт. ст.; $n = 17$). Средний возраст пациентов в первой группе составил $65,03 \pm 10,80$ лет, во второй — $63,50 \pm 8,31$ ($p = 0,576$). В первой группе преобладали женщины (64,1% против 35,3%, $p = 0,047$) и был меньше средний индекс массы тела ($26,30 \pm 1,38$ кг/м² против $32,20 \pm 4,15$ кг/м², $p = 0,02$). У пациентов обеих групп выполнялся забор венозной крови натощак утром и через 2 ч после приема АГП для оценки их концентрации методом высокоэффективной жидкостной хроматографии. Аналитический диапазон для лизиноприла, индапамида амлодипина составил 5–500 нг/мл, для валсартана — 10–10 000 нг/мл.

Результаты. Впервой группе средняя равновесная концентрация лизиноприла была выше в 2,67 раза ($p = 0,053$), а концентрация индапамида через 2 ч после его приема — выше в 1,83 раза ($p = 0,084$); при нормировании на дозу различия нивелировались ($p > 0,05$). Концентрации амлодипина и валсартана как до, так и через 2 ч после приема между группами не различались ($p > 0,05$). У 3-х из 39 (7,7%) пациентов с контролируемой АГ и у одного из 17 пациентов (5,9%, $p = 1,0$) с неконтролируемой АГ в сыворотке крови детектировались АГП, которые пациентам не назначались.

Выводы. Результаты пилотной части исследования ($n = 56$) продемонстрировали отсутствие различий средних концентраций изучаемых АГП в сыворотке крови у пациентов с контролируемой и неконтролируемой АГ, а также в ряде случаев наличие следов не назначенных врачом АГП.

Ключевые слова: артериальная гипертензия; антигипертензивные препараты; ВЭЖХ МС/МС; равновесная концентрация; лизиноприл; валсартан; амлодипин; индапамид

Для цитирования:

Селезнев С.В., Якушин С.С., Мыльников П.Ю., Транова Ю., Шулькин А.В., Якушева Е.Н., Никулина Н.Н. Терапевтический лекарственный мониторинг при неконтролируемой артериальной гипертензии: результаты пилотной части исследования // Российский медико-биологический вестник имени академика И. П. Павлова. 2023. Т. 31, № 2. С. 195–202. DOI: <https://doi.org/10.17816/PAVLOVJ119880>

DOI: <https://doi.org/10.17816/PAVLOVJ119880>

Therapeutic Drug Monitoring in Uncontrolled Arterial Hypertension: Result of the Pilot Part of Study

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ABSTRACT

INTRODUCTION: Despite the recently established evidence-based and systemic approach to treatment for arterial hypertension (AH), not in all cases its control can be achieved.

AIM: To conduct a comparative analysis of the concentration of antihypertensive drugs (AHTDs) in blood serum of patients with controlled and uncontrolled AH.

MATERIALS AND METHODS: Fifty six patients were included. Inclusion criteria: age ≥ 18 years, signing of informed consent, established diagnosis of AH, regular intake of any two of study antihypertensive drugs (lisinopril, amlodipine, valsartan) and also of indapamide at stable doses, for women — adequate contraception. According to the results of daily monitoring of the arterial pressure (AP), patients were divided into two groups: the first group — controlled hypertension (AP $< 140/90$ mmHg; $n = 39$), the second — uncontrolled hypertension (AP $\geq 140/90$ mmHg; $n = 17$). The mean age of patients in the first group was 65.03 ± 10.80 years, in the second — 63.50 ± 8.31 ($p = 0.576$). In the first group, women prevailed (64.1% vs. 35.3%, $p = 0.047$) and the mean body mass index was lower (26.30 ± 1.38 kg/m² vs. 32.20 ± 4.15 kg/m², $p = 0.02$). In patients of both groups, venous blood was taken in fasting condition in the morning and 2 hours after intake of AHTDs to assess their concentration by high-performance liquid chromatography. The analytical range for lisinopril, indapamide, amlodipine was 5–500 ng/ml, for valsartan — 10–10,000 ng/ml.

RESULTS: In the first group, equilibrium concentration of lisinopril was 2.67 times higher ($p = 0.053$), and concentration of indapamide in 2 hours after intake was 1.83 times higher ($p = 0.084$); when normalized to the dose, the differences were leveled out ($p > 0.05$). Concentrations of amlodipine and valsartan did not differ between the groups both before and 2 hours after intake ($p > 0.05$). In 3 of 39 (7.7%) patients with controlled hypertension and in one of 17 patients (5.9%, $p = 1.0$) with uncontrolled hypertension, AHTDs were detected in blood serum, which were not administered to them.

CONCLUSIONS: Results of the pilot part of the study ($n = 56$) demonstrated the absence of difference between the mean concentrations of the study AHTDs in the blood serum of patients with controlled and uncontrolled AH, and in some cases the presence of traces of AHTDs not administered by the doctor.

Keywords: arterial hypertension; antihypertensive drugs; HPLC MS/MS; equilibrium concentration; lisinopril; valsartan; amlodipine; indapamide

For citation:

Seleznev SV, Yakushin SS, Mylnikov PYu, Tranova Yu, Shchulkin AV, Yakusheva EN, Nikulina NN. Therapeutic Drug Monitoring in Uncontrolled Arterial Hypertension: Result of the Pilot Part of Study. *I. P. Pavlov Russian Medical Biological Herald*. 2023;31(2):195–202. DOI: <https://doi.org/10.17816/PAVLOVJ119880>

LIST OF ABBREVIATIONS

AH — arterial hypertension

AP — arterial pressure

HPLC-MS/MS — high-performance liquid chromatography tandem mass-spectrometry

INTRODUCTION

Arterial hypertension (AH) is one of the commonest diseases. Thus, according to the systematic analysis by K. T. Mills, et al., in 2010 the worldwide prevalence of AH was 31.1% [1]. According to the ESSE-RF study, in 2017, AH affected 44.2% of the Russian population.

Despite the recently established evidence-based and systemic approach to treatment for AH including modification of the lifestyle, development of five main groups of antihypertensive drugs (AHTDs), and recommendations on use of combined therapy as a starting therapy for the overwhelming majority of patients with AH, far not in all cases the target parameters of the arterial pressure (AP) can be achieved [2].

With this, in studying the mechanisms of inefficiency of the therapy, the attention is mostly paid to changes in the organism of patients, for example, hyperactivation of the renin-angiotensin- aldosterone system [3], sympathoadrenal system [4], modification of the targets for AHTDs [5]. At the same time, the pharmacokinetics of AHTDs in the ineffectiveness of the therapy is practically not studied. There are only single studies in which therapeutic drug monitoring was performed to evaluate patients' adherence to treatment [6].

It is logical to suggest that reduction of the content of AHTDs in blood below the minimal effective concentration can also make a significant contribution to the ineffectiveness of the therapy. This study was directed to checking this hypothesis.

The **aim** of this study to perform a comparative analysis of the concentration of antihypertensive drugs in blood serum of patients with controlled and uncontrolled AH.

MATERIALS AND METHODS

A *clinical, cross sectional, controlled* study was conducted on the clinical base of the Regional Clinical Cardiology Dispensary (Ryazan). The study has been approved by the Local Ethic Committee of the Ryazan State Medical University (Protocol No. 11 of 2022, March 04).

Inclusion criteria:

- age ≥ 18 years;
- signed Informed consent;

- diagnosis of AH established on the basis of Clinical guidelines 'Arterial Hypertension in Adults' (2020) approved by the Scientific and Practical Council of the Health Ministry of the Russian Federation:

- regular intake within a month of any two of the study AHTDs (Lisinopril, amlodipine, valsartan), and also of indapamide (possibly in fixed combinations) in stable dosages;

- for female patients of fertile age — observance of adequate contraception methods within the whole period of study.

Non-inclusion criteria:

- patients, directly or indirectly related to conduction of the study;

- patients who, for health reasons, cannot fill out a questionnaire by himself.

The study included a total of 56 patients who underwent hospital treatment for arterial hypertension. The patients underwent a routine clinical examination including anthropometry and measurement of 'office' arterial pressure (AP) using a mechanical tonometer. Within the study, each patient was daily taken AP (Cardiotekhnika-07-AD-3, Inkart), by the results of which the patients were divided to two groups:

- **first group** — patients with controlled AH (according to the given protocol, controlled AH was understood as AP $< 140/90$ mm Hg, $n = 39$);

- **second group** — patients with uncontrolled AH (AP $\geq 140/90$ mm Hg, $n = 17$).

The mean age of patients in first group was 65.03 ± 10.8 years, in the second 63.5 ± 8.31 ($p = 0.576$); in the second group there were more women (64.1% vs. 35.3%, $p = 0.047$), but lower body mass index (26.3 ± 1.38 kg/m² vs. 32.2 ± 4.15 kg/m², $p = 0.02$).

The level of systolic and diastolic AP in the group of uncontrolled AH was considerably higher than in the group of controlled AH. Patients of both groups were comparable in concomitant diseases, in used concomitant therapy, duration of AH, and also in medians of doses of study AHTDs (Table 1).

In patients of both groups, fasting venous blood was taken in the morning (20 ml) and in 2 hours after intake of an AHTD (10 ml). The blood was taken by puncture of a peripheral vein into 2 test tubes with yellow caps. The tubes were kept in the vertical position

Table 1. Characteristics of Patients and Analyzed Antihypertensive Therapy in Study Groups

Parameters	Controlled Arterial Hypertension	Uncontrolled arterial Hypertension	p
n	39	17	
<i>Clinical and Demographic Characteristics of Patients</i>			
Age, M ± SD, years	65.03 ± 10.80	63.50 ± 8.31	0.576
Body mass index, M ± SD, kg/m ²	26.30 ± 1.38	32.20 ± 4.15	0.020
Men, n	14	11	0.047
Systolic arterial pressure, M ± SD, mm Hg	124.0 ± 10.1	153.0 ± 11.4	< 0.001
Diastolic arterial pressure, M ± SD, mm Hg	70.3 ± 9.6	87.5 ± 10.8	< 0.001
<i>Mean Daily Doses of Study Antihypertensive Drugs</i>			
Lisinopril, Me (min; max), mg	20.0 (5.0; 40.0)	20.0 (10.0; 40.0)	0.120
Amlodipine, Me (min; max), mg	5.0 (2.5; 10.0)	10.0 (5.0; 10.0)	0.280
Indapamide, Me (min; max), mg	2.5 (1.5; 2.5)	2.5 (1.5; 2.5)	0.578
Valsartan, Me (min; max), mg	160.0 (160.0; 160.0)	160.0 (160.0; 160.0)	1.000

at room temperature for 15 minutes, then centrifuged at 2000 g–3000 g on Hettich EBA-20 centrifuge (Hettich Zentrifugen, Germany). After that, serum from each tube was poured to 4 cryotubes that were placed in a freezer for storage (at -70°C) to the moment of the analysis.

The concentration of the study AHTDs (Lisinopril, amlodipine, valsartan and indapamide) was determined by the method of high-performance liquid chromatography tandem mass-spectrometry (HPLC-MS/MS) by detection using Ultimate 3000 chromatograph and TSQ Fortis mass-spectrometer (ThermoFisher, USA) [7].

For sample preparation, acetonitrile was used with the addition of fexofenadine as an internal standard at a concentration of 1 ng/ml, which was added to blood serum samples in a ratio of 3:1 (600 µl of acetonitrile with fexofenadine and 200 µl of blood serum). The resulting mixture was shaken on a shaker for 1 minute, then centrifuged at 19,000 g (Avanti JXN-3, Beckman Coulter, USA) for 10 minutes at 4°C. The supernatant in the quantity of 600 µl of was pipetted into labeled vials and placed in an autosampler for subsequent analysis. The volume of the injected sample was 5 µl.

Separation was performed on a UCT Selectra column C18 4.6 mm × 100 mm, 3 µm, 100A (UCT, USA) with a pre-column Selectra C18 Guard Cartridges SLC-18GDC46-3UM (UCT, USA) at 35°C, in a gradient elution mode in ratio of 0.1% formic acid solution/acetonitrile: 0 min — 80%/20%, 0.1 min — 45%/55%, 5 min — 10%/90%, 10 min — 80%/20%, with a flow rate of 300 µl/min and detection in positive ionization mode by electrospray, electrospray voltage 4000 V, shell gas 50 arb, auxiliary gas 10 arb, purge gas 1 arb, evaporator temperature 350°C, ion-transporting tube — 300°C, using monitoring mode multiple reactions with an argon

feed rate of 2 mTorr.

The following transitions were used:

- **for indapamide:** 365.8 m/z → 117 m/z. 365.8 m/z → 131.4 m/z;

- **for Lisinopril:** 405.85 m/z → 84 m/z. 405.85 m/z → 245.4 m/z;

- **for amlodipine:** 409.2 m/z → 237.8 m/z. 409.2 m/z → 293.9 m/z;

- **for valsartan:** 436.2 m/z → 206.3 m/z. 436.2 m/z → 234.9 m/z.

Analytical range was:

- **for lisinopril:** 5–500 ng/ml,

- **for indapamide:** 5–500 ng/ml,

- **for amlodipine:** 5–500 ng/ml,

- **for valsartan:** 10–10,000 ng/ml.

The developed method was validated by the following parameters: selectivity, calibration curve, accuracy, precision, quantitative determination limit, sample transfer, sample stability, matrix effect.

The obtained results were processed in Statistica 13.0 program (Stat Soft Inc., USA; license number JPZ8111521319AR25ACD-W) and Excel for MAC ver. 16.24 (Microsoft, USA; ID 02984-001-000001).

The character of the distribution of the obtained data was evaluated by Shapiro–Wilk test. With normal distribution, Student's test was used to evaluate the statistical significance of the differences, Mann–Whitney test was used with the data distribution other than normal. The frequency parameters were compared using χ^2 criterion. With the normal distribution, the data were presented in the tables and graphs as arithmetic mean and standard deviation (M ± SD), or as median, minimum and maximum values with distribution other than normal (Me (min; max)).

RESULTS

About half of the patients with AH taking the study AHTDs (Lisinopril, amlodipine, valsartan, indapamide), *did not achieve therapeutic concentrations of at least one of these drugs in blood serum* (Table 2).

In patients with uncontrolled AH (second group), the equilibrium concentration (before intake of the drug) of Lisinopril was 2.67 times ($p = 0.053$) higher

than in patients with controlled AH (first group), and concentration of indapamide in 2 hours after intake was 1.83 times higher ($p = 0.084$). However, after recalculation of these parameters to the taken dose of the AHTD ('normalizing to the doze'), the differences between the groups leveled out ($p > 0.05$, Table 3). The concentrations of the other two study drugs (amlodipine and valsartan) did not differ between the groups both before and in 2 hours after intake of these AHTDs.

Table 2. Number of Patients in Whose Blood Serum Therapeutic Concentration of Study Drugs Was Not Achieved

Drugs	Controlled Arterial Hypertension	Uncontrolled Arterial Hypertension	p
Lisinopril, % of patients taking this drug	26.9	13.0	0.29
Valsartan, % of patients taking this drug	60.0	0	1.0
Amlodipine, % of patients taking this drug	23.3	29.2	0.75
Indapamide, % of patients taking this drug	26.1	21.4	0.74
Share of patients in whom at least one of the study drugs did not achieve the therapeutic concentration, %	46.0	52.0	0.79

Table 3. Concentrations (Me (min; max), ng/ml) of Antihypertensive Drugs in Fasting Blood Serum and in Two Hours after Intake of Drug

Drugs and Time of Taking Blood Biosample	Controlled Arterial Hypertension	Uncontrolled Arterial Hypertension	p
Lisinopril, fasting condition	47.0 (0.0; 473.6)	125.8 (0.0; 557.9)	0.053
Lisinopril, 2 hours after intake	100.3 (0.0; 474.9)	169.9 (0.0; 1112.8)	0.177
Lisinopril in fasting condition recalculated to the dose	1.89 (0.0; 36.3)	4.2 (0.0; 15.8)	0.100
Lisinopril in 2 hours after intake recalculated to the dose	5.69 (0.0; 47.49)	7.0 (0.0; 29.1)	0.297
Amlodipine, fasting condition	6.97 (0.0; 26.55)	7.9 (0.0; 19.9)	0.781
Amlodipine, 2 hours after intake	8.4 (0.0; 23.4)	9.47 (0.0; 16.5)	0.797
Amlodipine in fasting condition recalculated to the dose	1.02 (0.0; 5.31)	0.97 (0.0; 2.37)	0.934
Amlodipine in 2 hours after intake recalculated to the dose	1.12 (0.0; 4.69)	1.15 (0.0; 3.17)	0.724
Indapamide, fasting	8.39 (0.0; 38.7)	9.59 (0.0; 17.6)	0.640
Indapamide, 2 hours after intake	12.4 (0.0; 77.85)	22.72 (0.0; 39.18)	0.084
Indapamide in fasting condition recalculated to the dose	5.05 (0.0; 21.4)	3.89 (0.0; 10.97)	0.420
Indapamide in 2 hours after intake recalculated to the dose	7.07 (0.0; 39.3)	11.63 (0.0; 15.67)	0.110
Valsartan, fasting	175.48 (0.0; 521.3)	611.9 (488.12; 735.77)	0.190
Valsartan, 2 hours after intake	608.63 (174.1; 1353.9)	1463.5 (1317.7; 1609.4)	0.267

In 17 of 39 patients (43%) with controlled AH, concentration of at least one of taken AHTD was below the limit of quantitative determination. In the group with uncontrolled AH, the number of such patients was 5 of 17 (29%) ($p = 0.58$).

It was also found in the course of study that in blood serum of 3 of 39 (7.7%) patients with controlled AH (first group) and of one of 17 patients (5.9%), 1.0, with uncontrolled AH (second group), AHTDs were detected that were not prescribed.

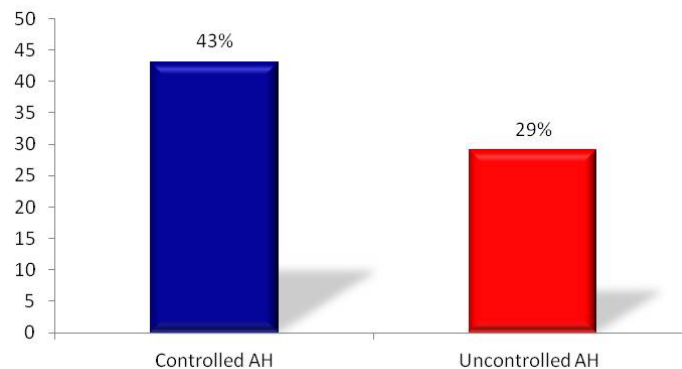


Fig. 1. Share (%) of patients with concentration of at least one of taken antihypertensive drugs below the level of quantitative determination ($p = 0.318$).

DISCUSSION

Optimal drug treatment of hypertension is of great importance for reducing the incidence of cardiovascular and kidney diseases, as well as of mortality from them [8, 9]. The inability to achieve the target AP values, despite the use of three or more AHTDs (including a diuretic) in the maximum tolerated doses and with obligatory observing the recommended regimen of non-drug measures, is defined as *resistant hypertension* [10]. However, according to the literature, up to 50% of patients with verified resistant hypertension *do not follow the treatment regimen* [11, 12].

In the pilot part of the study, the hypothesis of the effect of the pharmacokinetics of AHTD on the ineffectiveness of AH therapy was initially tested. With this, to standardize the methodology, the most frequently used representatives of three main groups of AHTDs were selected as the study AHTDs (in the practice of the clinical base of the study): of blockers of the renin-angiotensin-aldosterone system — valsartan or Lisinopril, of blockers of slow calcium channels — amlodipine, of diuretics — indapamide.

The results obtained, firstly, demonstrated that in half the patients with AH, the taken AHTDs (Lisinopril, amlodipine, valsartan, indapamide), regardless of achievement/non-achievement of AH control with this therapy, *do not achieve therapeutic concentrations in blood serum* (Table 2) which is a potential opportunity to increase the effectiveness of this therapy.

Secondly, it was shown that concentrations of the study AHTDs in patients with uncontrollable AH, are not only not less than in patients with controlled AH, but even higher for indapamide and Lisinopril (Table 3). The differences revealed may probably be related to a higher dose of these AHTDs taken by patients with uncontrolled AH, which is evidenced by their leveling out in recalculation to the dose taken (Table

3). On the other hand, the mean daily doses of these drugs were comparable in the study groups (Table 1). This contradiction requires further study within this scientific trend with increase in the statistical power and introduction of the analysis of additional factors.

Thirdly, in blood serum of a number of patients undergoing hospital treatment, AHTDs were found not recommended by the doctor either before or during hospitalization, which is probably associated with self-treatment of patients (as an 'addition' to prescribed treatment), but this hypothesis also requires verification at subsequent stages of the study.

CONCLUSIONS

1. There is no difference in concentration of antihypertensive drugs (amlodipine, valsartan) in blood serum of patients with controlled and uncontrolled arterial hypertension.

2. The equilibrium concentration of Lisinopril in blood serum and concentration of indapamide in 2 hours after intake in patients with uncontrolled arterial hypertension 2.67 times ($p = 0.053$) and 1.83 times ($p = 0.084$), respectively, exceeded the analogous parameters in patients with control of the arterial pressure. After recalculation of the concentrations of the antihypertensive drug to the dose taken, the reliable differences level out.

3. Both in the group of patients with controlled arterial hypertension and in the group with uncontrolled arterial hypertension, the patients were identified with concentrations of the study drugs in blood serum below the therapeutic level (in 46.0% of patients with controlled AH and in 52.0% with uncontrolled AH, $p = 0.79$).

4. In blood serum of some patients of the group of controlled and of the group of uncontrolled arterial hypertension (7.7% and 5.9%, respectively, $p = 1.0$) antihypertensive drugs were found that were not administered to them either before or during inpatient treatment.

ADDITIONALLY

Funding. The work was supported by the grant of the President of the Russian Federation No.MD-13.10.2022.3.

Conflict of interests. The authors declare no conflicts of interests.

Contribution of the authors: S. V. Seleznev — collection and processing of clinical material, formation of a database of blood samples; S. S. Yakushin — research concept, editing the text; P. Yu. Mylnikov, Yu. Tranova — conducting HPLC MS/MS studies; A. V. Shchul'kin — data evaluation and interpretation; E. N. Yakusheva — research design, writing and editing the text; N. N. Nikulina — editing the text. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Финансирование. Работа поддержана грантом Президента РФ № МД-13.10.2022.3.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Вклад авторов: Селезнев С. В. — сбор и обработка клинического материала, формирование базы биообразцов крови; Якушин С. С. — концепция исследования, редактирование текста; Мыльников П. Ю., Транова Ю. — проведение исследований ВЭЖХ-МС/МС; Щулькин А. В. — оценка и интерпретация данных, написание текста; Якушева Е. Н. — дизайн исследования, написание и редактирование текста; Никулина Н. Н. — редактирование текста. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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