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RESEARCH OF 1,3-OXAZOLE-4-IL-PHOSPHONIC ACID DERIVATIVE ON THE CONTENT OF FATTY ACIDS OF LIPIDS IN RATS WITH ARTERIAL HYPERTENSION

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Кількість хворих з артеріальною гіпертензією (АГ) продовжує збільшуватись. Суттєвим негативним наслідком артеріальної гіпертензії є структурні, метаболічні та функціональні порушення у тканинах міокарду, судин та інших органів, зокрема зміна вмісту жирних кислот (ЖК) та їх співвідношення.

***Мета роботи** – дослідити зміну жирнокислотного складу ліпідів сироватки крові та тканин щурів з артеріальною гіпертензією під дією нової оригінальної сполуки - похідного 1,3-оксазол-4-іл-фосфонової кислоти (скорочена назва - похідне оксазолу).*

***Матеріали та методи.** Дослідження проводили на білих статевозрілих щурах. Артеріальну гіпертензію моделювали шляхом сольового навантаження – сольового пиття (1 % розчин натрію хлориду) з вільним доступом до нього впродовж 21 доби. Тваринам з 14-ї доби вводили похідне оксазолу в дозі 25 мг/кг внутрішньоочеревинно, один раз на добу, щоденно, протягом 7 діб. Вміст ЖК ліпідів відцентрифугованої сироватки крові та гомогенізованих у 0,9 % фізіологічному розчині NaCl тканин визначали за допомогою газохроматографічного аналізу.*

***Результати та їх обговорення.** Введення похідного оксазолу на фоні підвищеного артеріального тиску у щурів достовірно не впливало на суму НЖК та ННЖК в сироватці крові на відміну від групи щурів з АГ за рахунок тенденції до відновлення вмісту стеаринової кислоти, проте змінений вміст лінолевої та арахідонової кислот практично не відрізнявся від значень останніх в контрольній групі за даних умов експерименту. В аорті спостерігалось відновлення вмісту пальмітинової, стеаринової, лінолевої та арахідонової кислот. В серці встановлено зміну вмісту лінолевої та арахідонової кислот у зворотньому напрямку порівняно з контрольною групою.*

***Висновки.** Введення похідного оксазолу в дозі 25 мг/кг (ED_{50}) внутрішньоочеревинно один раз на добу протягом 7 днів при одночасному моделюванні артеріальної гіпертензії шляхом сольового навантаження вцілому не викликало негативних змін та призводило до відновлення ліпідних показників НЖК, ННЖК та ПНЖК*

***Ключові слова:** артеріальна гіпертензія, жирні кислоти,похідне 1,3-оксазол-4-іл-фосфонової кислоти, похідне оксазолу, щури*

1. Introduction

Today, the global pharmaceutical market presents a wide range of antihypertensive drugs. However, the number of patients with arterial hypertension (AH) continues to increase. This disease causes annually about 12.8 % of deaths in the world and leads to a significant deterioration in the quality of life of patients due to the severity of the consequences of its ineffective treatment: myocardial infarction, stroke, chronic renal failure and peripheral arterial disease [1, 2]. The accelerated dynamics of hypertension is an urgent problem of modern medicine, which is exacerbated by demographic aging of the population and behavioural risk factors, including malnutrition, hypodynamia, and permanent stress conditions [3].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Despite the presence of a significant arsenal of drugs with a different mechanism of action, the effectiveness of antihypertensive therapy remains low. In particular, in Ukraine, this figure is only 8.1 % in rural areas and 18.7 % in the urban population, which requires further detailed study of the pathogenesis of this disease and the search for new compounds to achieve the target blood pressure levels by acting directly on the target, which is the cause of development arterial hypertension [4, 5].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

Substantial negative effects of arterial hypertension are structural, metabolic and functional disorders in the tissues of the myocardium, vessels and other organs, in particular, changes in the content of fatty acids (FA) and their ratios [6, 7]. Changes in lipid metabolism in hypertension are associated with a decrease in the consumption of fatty acids by the body due to increased absorption and an imbalance between glucose and FA in mitochondria [8]. It is known that hypertension rats in blood plasma most change the content of arachidonic, palmitic, linoleic, pentadecanoic and margaric acids [9]. Therefore, an important task of modern antihypertensive therapy is the search for molecules and the development of new antihypertensive drugs, which can not only normalize blood pressure, but also correct these pathological changes.

4. The field of research considering the general problem, which is described in the article

The derivative of 1,3-oxazole-4-yl-phosphonic acid (abbreviated name - oxazole derivative) is a novel, original compound, which, according to the results of previous experimental studies, in vitro and in vivo has a vasodilating effect and is promising for further study as a

low-toxic antihypertensive agent, but its influence on the fatty acid composition of lipids in the blood to this time was not investigated [10, 11].

5. Formulation of goals (tasks) of article

The aim of the work was to investigate the changes in the fatty acid composition of blood serum lipids and tissues of rats with arterial hypertension under the action of oxazole derivatives.

6. Presentation of the main research material (methods and objects) with the justification of the results

Materials and methods. The studies were conducted on white, sexually mature rats with an average weight of 181.8±3.54 g. Animal rearing and care was carried out in accordance with the European Union Directive 2019/10/63 EU on the protection of vertebrate animals used for experimental and other scientific purposes and, accordingly, to the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruel Treatment" [12, 13].

Arterial hypertension (AH) was modelled with salt loading – salt drink (1 % solution of sodium chloride) with free access to it for 21 days [14]. The mean blood pressure level in non-sarcotised rats was recorded by sphygmomanometric method using a specialized cuff with a pulse sensor mounted on the rat's tail and an analysis of the periodicity of blood flow oscillations at the UgoBasile installation (Italy, 2005).

With the random sampling technique, rats were divided into 3 groups of 7 individuals in each. Group 1 included intact rats. Group 2 (blank) includes rats, which formed a model of stable AH during 21 days by salt loading. Group 3 includes rats with elevated blood pressure of 8 % and above at 14 days after the start of salt loading. Animals of this group from the 14th day were given a dose of 25 mg / kg intraperitoneally, once, daily for 7 days. This group of animals is formed to determine the effect of 1,3-oxazole-4-yl-phosphonic derivative in order to prevent the development of hypertension or decrease the degree of hypertension.

The rats were decapitated with subsequent extirpation of the heart, aorta, liver, kidneys and blood collection. The content of liquid lipids of centrifuged blood serum and homogenized in 0.9 % saline NaCl tissue was determined by gas chromatographic analysis according to the generally accepted method [15]. The peaks of fatty acids were identified by comparing with the time maintenance of the peaks of standard FA. An assay of the ratio of fatty acids of lipids in % was carried out by the method of normalizing the peaks of the peaks of ethylenic derivatives of FA [16].

Changes in fatty acid composition of serum lipids were evaluated by the definition of the quantitative content of the 9 most informative FA: myristic $C_{14:0}$, pentadecane $C_{15:0}$, palmitinic $C_{16:0}$, margaric $C_{17:0}$, stearic $C_{18:0}$, amounting to SFA, and oleic $C_{18:1}$, linoleic $C_{18:2}$, linolenic $C_{18:3}$, arachidonic $C_{20:4}$, amounting to the MUFA. Linoleic $C_{18:2}$, linolenic $C_{18:3}$ and arachidonic $C_{20:4}$ FA belong to the sum of polyunsaturated fatty acids (PUFA) and are defined as irreplaceable [15].

Statistical data was processed using the BioStat 2009 v 5.8.4 licensing program (produced by Analyst Soft). To compare mean values of the samples, a simple Student's coefficient was used, or a two-sample t-test with different dispersions (heteroscedastic). Changes in indicators were considered statistically significant at a significance level of more than 95 % ($P<0.05$).

Results of the research. Studies have shown that in the modelling of persistent arterial hypertension by the salt load in Group 2, the fatty acid composition of blood serum lipids and tissues of the investigated organs significantly changed in comparison with the group of normotensive intact rats (Tab.1). In particular, serum levels of stearic acid increased by 28.4 % ($p<0.05$), resulting in an increase in the amount of SFA by 11.2 % ($p <0.05$). At the same time, the content of arachidonic acid increased by almost 5 times ($p <0.05$), but the amount of UFA and PUFA decreased in the form of a tendency due to a decrease in the content of linoleic acid. In the aorta, an increase in the content of myristic (by 8 times, $p<0.05$) and palmithinic acid (40.4 %, $p<0.05$) and reduction in the content of stearic acid (17.8 %, $p<0.05$), linoleic (28.9 %, $p<0.05$) and arachidone (25.4 %, $p<0.05$) acids. Accordingly, an increase in the amount of SFA and a reduction in the amount of UFA, PUFA in the aorta were noted. In the heart, only a decrease in the content of linoleic and an increase in the content of arachidonic acids was observed, respectively, by 25.8 % ($p <0.05$) and 16.9 % ($p <0.05$), and in the liver the increase in the content of oleic (17.1 %, $p <0.05$), linoleic acids (by 29.1 %, $p <0,05$) and reduction of arachidonic acid content (by 28,6 %, $p<0.05$). At the same time, in the kidneys, a 22.2 % ($p<0.05$) decrease in the amount of SFA was observed due to myristic and palmitic acid and a corresponding increase in the UFA value by 16.7 % ($p <0.05$) due to oleic, linoleic and arachidonic acids .

From Tabl. 2, it can be seen that the administration of the oxazole derivative in the background of elevated blood pressure in rats did not significantly affect the amount of SFA and UFA in serum, unlike the group of rats with hypertension due to the tendency to restore the stearic acid content, but the changed content of linoleic and arachidonic acids was virtually nonexistent it differed from the values of the latter in the blank group under the given experimental conditions. Restoration of the content of stearic, linoleic and arachidonic acids in the aorta and reduction of the palmitic acid content to the baseline level was observed. In the heart, the change in the content of linoleic and arachidonic acids in the reverse direction compared with the blank group was established. Thus, the content of linoleic acid, by contrast, was higher by 14.4 % ($p <0.05$), and the content of arachidonic acid was lower by 18.4 % ($p <0.05$) compared to normalizing rats. In the kidneys and the liver, all the lipid fatty acid composition was normalized.

Table 1

Fatty acid composition of rat lipid tissues and serum in experimental arterial hypertension, % (M±m, n=7)

Nomenclature of FA	blood serum		aorta		heart		kidneys		liver	
	Group No.2	Group No.1	Group No.2	Group No.1	Group No.2	Group No.1	Group No.2	Group No.1	Group No.2	Group No.1
Myristic C14:0	0.3±0.1	0.3±0.1	3.3±0.5*	0.4±0.1	0.6±0.1	0.4±0.1	1.1±0.1*	3.1±0.5	0.4±0.1	0.3±0.1
Pentadecane C15:0	0.4±0.1	0.2±0.1	0.3±0.1	0.5±0.1	1.6±0.3	1.6±0.5	0.4±0.1	0.4±0.1	0.4±0.1	0.3±0.1
Palmitinic C16:0	26.4±1.3	25.3±1.5	38.6±1.3*	27.5±1.5	19.5±1.5	18.3±1.5	21.2±1.0*	29.4±1.5	19.1±0.1	21.3±1.3
Margaric C17:0	0.4±0.1	0.3±0.1	0.3±0.1	0.4±0.1	0.6±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.3±0.1
Stearic C18:0	11.3±1.0*	8.8±1.0	11.1±1.0*	13.5±1.0	9.3±0.5	9.0±1.0	10.2±0.5	9.5±0.5	6.6±0.5	6.1±0.5
Oleic C18:1	15.2±1.0	15.6±1.3	18.4±0.6	18.7±0.7	15.3±0.7	13.9±1.0	14.8±0.7*	17.2±1.0	15.1±1.0*	12.9±1.0
Linoleic C18:2	44.2±1.5*	49.0±1.5	23.1±1.0*	32.5±1.5	22.1±1.0*	29.8±1.5	24.8±0.5*	28.1±1.5	35.9±1.5*	27.8±1.5
Linolenic C18:3	0.4±0.1	0.2±0.1	0.3±0.1	0.5±0.1	0.6±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.5±0.1
Arachidonic C18:4	1.4±0.5*	0.3±0.1	4.4±0.5*	5.9±0.8	30.5±1.0*	26.1±1.5	26.7±1.0*	11.3±1.0	21.7±1.5*	30.4±1.5
∑SFA	38.8±1.8*	34.9±1.8	53.6±1.5*	42.3±1.6	31.6±2.0	29.7±1.8	33.3±1.5*	42.8±2.0	26.9±1.6	28.3±1.8
∑UFA	61.2±1.8	65.1±1.8	46.4±1.5*	57.7±1.6	68.5±2.0	70.3±1.8	66.5±1.5*	57.0±2.0	73.1±1.6	71.7±1.8
∑PUFA	46.0±1.5*	49.5±1.5	27.8±1.3*	38.9±1.5	53.2±1.8	56.3±1.6	51.7±1.3*	39.8±1.6	58.0±1.3	58.7±1.5

*Note: * – p <0.05 relative to the intact group (group No. 1)*

Table 2

Influence of 1,3-oxazole-4-yl-phosphonic acid derivative on fatty acid composition of rat lipid tissues and serum in experimental arterial hypertension, % (M±m, n=7)

Nomenclature of FA	blood serum		aorta		heart		kidneys		liver	
	Group No.2	Group No.1	Group No.2	Group No.1	Group No.2		Group No.2	Group No.1	Group No.2	Group No.1
Myristic C14:0	0.5±0.1	0.3±0.1	3.1±0.5*	0.4±0.1	0.4±0.1	0.4±0.1	2.4±0.5	3.1±0.5	0.3±0.1	0.3±0.1
Pentadecane C15:0	0.5±0.1	0.2±0.1	0.4±0.1	0.5±0.1	1.1±0.5	1.6±0.5	0.4±0.1	0.4±0.1	0.3±0.1	0.3±0.1
Palmitinic C16:0	28.3±1.0	25.3±1.5	30.1±1.5	27.5±1.5	17.4±1.0	18.3±1.5	24.6±1.0*	29.4±0.1	20.8±1.0	21.3±1.3
Margaric C17:0	0.5±0.1	0.3±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.3±0.1	0.3±0.1
Stearic C18:0	10.9±0.5	8.8±1.0	14.0±1.0	13.5±1.0	8.4±1.0	9.0±0.1	10.8±0.5	9.5±0.5	8.4±0.7	6.1±0.5
Oleic C18:1	14.8±0.6	15.6±1.3	18.1±1.0	18.7±0.7	16.3±0.5	13.9±1.0	19.2±0.8	17.2±1.0	14.5±1.0	12.9±1.0
Linoleic C18:2	42.2±1.0*	49.0±1.5	28.0±1.5*	32.5±1.5	34.1±1.0*	29.8±1.5	31.4±0.5	28.1±1.5	30.1±1.3	27.8±1.5
Linolenic C18:3	0.6±0.1*	0.2±0.1	0.4±0.1	0.5±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.5±0.1
Arachidonic C18:4	1.5±0.5*	0.3±0.1	5.5±0.5	5.9±0.8	21.3±1.0*	26.1±1.5	10.3±1.0	11.3±1.0	24.9±1.5	30.4±1.5
∑SFA	40.7±1.5	34.9±1.8	48.0±1.8*	42.3±1.6	27.7±2.0	29.7±1.8	38.6±1.5	42.8±2.0	30.1±1.5	28.3±1.8
∑UFA	59.1±1.5	65.1±1.8	52.0±1.8	57.7±1.6	72.1±2.0	70.3±1.8	61.3±1.5	57.0±2.0	69.9±1.5	71.7±1.8
∑PUFA	44.3±1.3*	49.5±1.5	33.9±1.5*	38.9±1.5	55.8±1.8	56.3±1.6	42.1±1.3	39.8±1.6	55.4±1.3	58.7±1.5

*Note: * – p <0.05 relative to the intact group (group No. 1)*

Discussion of results. The established fact of increasing the amount of SFA in the kidneys compared with the blank group after the administration of the 1,3-oxazole-4-yl-phosphonic acid derivative may indicate the ability of the compound to stabilize cell membranes and inhibit free radical oxidation during the development of modulation-induced arterial hypertension inositol lipid cycle and signal system of the cell [17].

The effect of the oxazole derivative on the increase of arachidonic acid content by 25.0 % (p <0.05) in comparison with hypertensive rats in the aorta may be related to one of the mechanisms of vasodilating effect of the test compound, since arachidonic acid acts as a precursor in the synthesis of prostaglandin E2 (PGE2), which, in turn, interacts with receptors of type EP2, causes vasodilation [18]. At the same time, it is logical to increase the content of linoleic acid in the aorta as a precursor to the synthesis of arachidone. On the other hand, a decrease in the content of the latter in the heart and kidneys after the introduction of the derivative of oxazole may indicate the restorative ability of the test compound to reduce lipid peroxidation in the abovementioned tissues. A similar effect was found in β-blockers that exhibit cardioprotective and nephroprotective effects [9, 19].

7. Conclusions from the conducted research and prospects for further development of this field

1. Conducted studies showed a pronounced effect of 1,3-oxazole-4-yl-phosphonic acid derivative on fatty acids of serum lipids of blood and tissues of rats with elevated blood pressure in the modelling of arterial hypertension by salt loading.

2. The introduction of the test compound at a dose of 25 mg / kg (ED_{50}) intraperitoneally once daily for 7 days with simultaneous simulation of arterial hypertension by salt load did not cause any adverse changes in general and led to the restoration of lipid parameters of SFA, UFA and PUFA.

3. The established fact of the influence of the derivative of oxazole on the composition of FA lipids is the basis for further study of its mechanisms of action with a possible prospect of studying as an antihypertensive drug.

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Aim. *Spectrophotometry is one of the most widely used methods in the pharmaceutical analysis. The main advantages of this absorption method are the highly sensitive, cost-effective and available to quality control laboratories for dosage forms. However, there is a need to find new analytical reagents. Therefore, the aim of the present work was investigation and development of spectrophotometric method based on reaction with p-chloranil for the determination of meldonium dihydrate in dosage forms.*

Methods. *In the study were used working standard of meldonium dihydrate, p-chloranil, DMF, the sample of finished dosage forms. Absorption of the reaction products was measured using spectrophotometer Specord 200.*

Results. *The optimum conditions of the spectrophotometric analysis has been established during the process of development this procedure. The influence of various parameters such as nature of the solvent, concentration of reagent, temperature, time of heating were investigated. It was experimentally established that meldonium dihydrate reacts with p-chloranil in DMF medium to form the coloured reaction product with absorption maximum at 556 nm. The proposed method was subjected to validation tests. The method was validated for the parameters like linearity, precision, accuracy, robustness and range of application. Beer's law was performed at the concentration range of 8.00–20.00 mg/100 ml with correlation coefficient 0.9995. The linearity ranges were calculated with the help of regression analysis by means of least squares. The proposed procedure meets the requirements of State Pharmacopoeia of Ukraine.*

Conclusions. *The spectrophotometric method for the determination of meldonium dihydrate was developed and validated. This procedure is successfully applied for dosage forms analysis. Results of the study showed that the procedure is accurate, simple and relevant for application at the quality control laboratories for dosage forms*

Keywords: *spectrophotometry, derivatives of quinone, p-chloranil, meldonium dihydrate, analysis, quantitative determination, validation*

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RESEARCH OF 1,3-OXAZOLE-4-IL-PHOSPHONIC ACID DERIVATIVE ON THE CONTENT OF FATTY ACIDS OF LIPIDS IN RATS WITH ARTERIAL HYPERTENSION

p. 28-31

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The number of patients with arterial hypertension (AH) continues to increase. Significant negative effects of arterial hypertension are structural, metabolic and functional disorders in the tissues of the myocardium, vessels and other organs, in particular, changes in the content of fatty acids (FA) and their correlation. The purpose of the study is to investigate the change in fatty acid composition of lipids in blood serum and tissues of rats with arterial hypertension under the influence of a new original compound, 1,3-oxazole-4-yl-phosphonic acid derivative (abbreviated name – oxazole derivative).

Materials and methods. *The studies were conducted on white, sexually mature rats. Arterial hypertension was modeled by salt load – salt drink (1 % solution of sodium chloride) with free access to it for 21 days. Animals from the 14th day received oxazole derivative at a dose of 25 mg / kg intraperitoneally, once daily, for 7 days. The content of fatty acids of centrifuged blood serum and homogenized in 0.9 % saline NaCl tissue was determined by gas chromatographic analysis.*

Results and discussion. *The administration of oxazole derivative in the background of increased blood pressure in rats did not significantly affect the amount of SFA and USFA in serum in contrast to*

the group of rats with hypertension due to the tendency to restore the stearic acid content, but the changed content of linoleic and arachidonic acids practically did not differ from the values in the blank group. There was a restoration of the content of palmitic, stearic, linoleic and arachidonic acids in aorta. In heart, the change in the content of linoleic and arachidonic acids in the reverse direction compared with the blank group was established.

Conclusions. *The administration of 25 mg/kg (ED_{50}) of oxazole derivative intravenous intraperitoneally once daily for 7 days with simultaneous simulation of arterial hypertension by salt load did not cause any adverse changes and led to the restoration of lipid parameters of SFA, USFA and PUFA*

Keywords: *arterial hypertension, fatty acids, 1,3-oxazole-4-yl-phosphonic acid derivative, oxazole derivative, rats*

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THE RESEARCH OF FREE AMINOACIDS OF WATER-SOLUBLE PROTEIN-POLYSACCHARIDE COMPLEX OF OYSTER MUSHROOM PLEUROTUS OSTREATUS

p. 32-37

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