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Short Communication

Efficiency of the application of the 1.3-oxazole-4-il-phosphonic acid derivative on the sustained arterial hypertension model in rats

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ABSTRACT

The actual direction of modern pharmacology lies in the search for new biologically active compounds with antihypertensive action for the further development of original drugs. The 1.3-oxazole-4-il-phosphonic acid derivative is a new original compound, which, according to the previous experimental studies *in vitro*, has vasodilatory activity and is promising for further study as an antihypertensive agent. The purpose of the paper is to study the effectiveness of the 1.3-oxazole-4-il-phosphonic acid derivative for the prophylaxis and treatment of arterial hypertension, modeled in unanesthetized rats. The studies were carried out in white Wistar rats. Sustained arterial hypertension was modeled by salt loading with free access to a salt drink of 1% sodium chloride solution for 21 days. Mean arterial pressure (MAP) and heart rate in unanesthetized rats were recorded using a sphygmomanometric method with the help of a specialized cuff with a heart rate sensor mounted on the rat's tail and a frequency analysis of blood flow oscillations. On intraperitoneal administration of the 1.3-oxazole-4-il-phosphonic acid derivative at the dose of 25 mg/kg for 7 days in normotensive unanesthetized rats, the mean arterial pressure remained practically unchanged, with the heart rate rising by 12.0% on the 7th day ($P < 0.05$), which could be due to the inclusion of compensatory mechanisms for the cardiovascular system regulation. In the treatment regimen of single intraperitoneal administration of 25 mg/kg oxazole derivative to the rats with saline-induced arterial hypertension for 7 days, the studied compound showed a pronounced hypotensive effect. The latent period of the test substance is 30-40 minutes. On the first day after administration of the oxazole derivative, the mean arterial pressure decreased by 27.0% ($P < 0.05$), and on the 7th day by 19.4% ($P < 0.05$) relative to the data recorded in animals with arterial hypertension. The hypotensive effect of the oxazole derivative is comparable to the effect of amlodipine, the test compound being non-toxic unlike amlodipine, since the LD_{50} of the oxazole derivative is 5 times higher than amlodipine. In conditions of salt load, the test compound prevents the formation of arterial hypertension. 7-day administration of the oxazole derivative against a background of elevated mean arterial pressure shows a hypotensive effect and normalizes heart rate.

KEYWORDS: arterial hypertension, heart rate, antihypertensive pharmacological agents, 1.3-oxazole-4-il-phosphonic acid derivative.

INTRODUCTION

Arterial hypertension is an important medical and social problem of the present time, as it is defined as one the most important risk factors for cardiovascular diseases, and it has reached the scale of epidemic in economically developed countries of the world [1, 2]. Thanks to the development of healthcare

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system the global pharmaceutical market offers a wide range of antihypertensive agents. However, the number of patients with uncontrolled and resistant arterial hypertension continues to increase [3]. For this reason, the actual direction of modern pharmacology lies in the search for new biologically active compounds with antihypertensive action for the further development of original drugs.

The 1.3-oxazole-4-il-phosphonic acid derivative (a reduced oxazole derivative) is a new original compound, which, according to the previous experimental studies *in vitro*, has vasodilatory activity and is promising for further study as an antihypertensive agent [4]. Safety of the oxazole derivative has been confirmed by the results of acute toxicity studies in mice of both sexes with intraperitoneal administration. It has been established that the studied compound belongs to the toxicity class VI, which implies that they are 'relatively safe compounds' [5].

The purpose of the paper is to study the effectiveness of the 1.3-oxazole-4-il-phosphonic acid derivative for the prophylaxis and treatment of arterial hypertension, modeled in unanesthetized rats.

MATERIALS AND METHODS

The studies were carried out in 81 mature white Wistar rats with an average weight of 181.8 ± 3.54 g. All manipulations with animals were carried out according to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986).

Sustained arterial hypertension (AH) was modeled by salt loading with free access to a salt drink of 1% sodium chloride solution for 21 days [6]. The rats that showed an increase in MAP by 10% and above were considered as animals with the induced AH. Animals that did not demonstrate an increase in MAP 21 days after the initiation of salt load prior to allocation were not included and removed from the experiment.

All rats were kept in the identical laboratory conditions on regular vivarium diet in the day/night mode at the temperature of 20-22 °C and a free access to drinking water. Mean arterial pressure and heart rate in unanesthetized rats were recorded using a sphygmomanometric method with the help of a specialized cuff with a heart rate sensor mounted on the rat's tail and a frequency analysis of blood flow oscillations at the Ugo Basile setting (Italy, 2005). Laboratory rats were preheated to the temperature of 28-32 °C for 10-15 minutes and maintained in the indicated temperature throughout the experiment to ensure blood circulation in the tail in the required volume and blood flow stabilization.

The rats were randomized to six groups of 12-15 individuals in each.

Group No. 1 included intact rats, i.e. animals without any salt load and without other manipulations (administration of drugs, etc.) with a free access to drinking water.

Group No. 2 included animals that did not have any salt load with a free access to drinking water and once daily for 7 days intraperitoneally administered with the 1.3-oxazole-4-il-phosphonic acid derivative at the dose of 25 mg/kg (ED_{50}).

Group No. 3 (blank) included rats, in which the sustained AH was modeled by salt loading for 21 days.

Group No. 4 included rats, which, on the background of the induced AH on the 21st day from the initiation of salt load once daily for 7 days, were given the test compound intraperitoneally at the dose of 25 mg/kg.

Group No. 5 included animals, which, on the background of the induced AH, were given a comparator – amlodipine, a slow calcium channel blocker at the therapeutic dose of 1.5 mg/kg body weight. Amlodipine was administered on the 21st day from the initiation of salt load once daily for 7 days [7].

Group No. 6 included rats with elevated mean arterial pressure of 8% and above on the 14th day after the initiation of salt load. Animals of this group from the 14th day were given an oxazole derivative intraperitoneally at the dose of 25 mg/kg once daily, for 7 days. This group of animals was created to determine the effect of the 1.3-oxazole-4-il-phosphonic acid derivative in preventing the development of AH or reducing the degree of hypertension.

RESULTS AND DISCUSSION

Physiological growth of body weight was observed in all study groups. However, no statistically

significant difference was found between the groups (Figure 1).

In group No. 1 (intact rats), cardiovascular system activity during 21 days of follow-up did not demonstrate any significant fluctuations and alterations (Tables 1, 2).

In group No. 2, in conditions of administration of the oxazole derivative intraperitoneally to the intact animals at the dose of 25 mg/kg once a day for seven days, mean arterial pressure on the 1st and 7th days practically corresponded to the baseline value. At the same time, previous studies in anesthetized normotensive rabbits showed no significant changes in MAP after administration of the test compound at the dose of 25 mg/kg [8]. At the same time, heart rate on the first day after administration of the test compound was almost unchanged, but after measurements on the 7th day, the test indicator increased by 12.0% ($P < 0.05$) compared with the baseline value. Such a reaction can be connected with the inclusion of compensatory mechanisms for regulating the cardiovascular system activity in normotensive rats, in particular by activating the sympathetic nervous system [9]. At the same time, a similar effect of heart rate acceleration was investigated in the α-adrenergic blocker prazosin [10].

In the blank group No. 3, salt load resulted in the formation of AH for 21 days, as was indicated by an increase in mean arterial pressure by 24.6% ($P < 0.05$) relative to the baseline data, but it did not significantly affect the heart rate in rats.

In group No. 4, a tendency towards decrease in mean arterial pressure was observed 30 minutes after intraperitoneal administration of the test compound to the animals at the dose of 25 mg/kg body weight. Hypotensive action of the compound intensified over time and in 3 h, there was a decrease in MAP by 14% ($P < 0.05$) relative to the data recorded in animals on the 21st day of salt load. The effect of the test compound was maintained and increased significantly during 24 hours after single administration, as shown by a decrease in MAP by 27.0% ($P < 0.05$) relative to the data recorded in animals with AH. A similar effect was observed after administration of amlodipine against the background of arterial hypertension in group No. 5. However, mean arterial pressure decreased to a lesser extent by 23.1% ($P < 0.05$). At the 7th day of administration of the test compound in

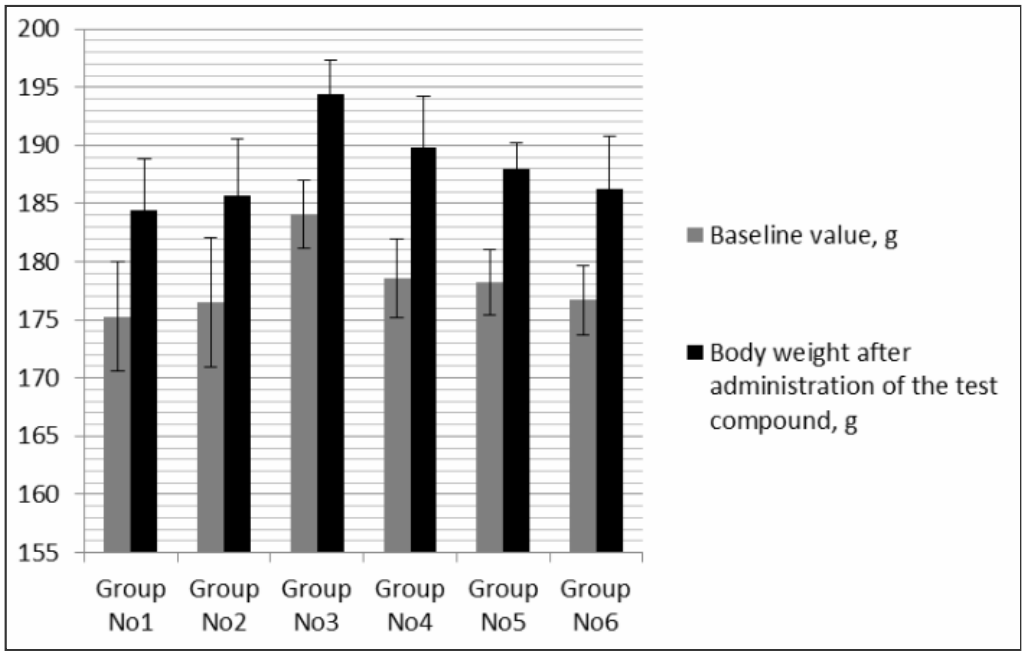

Figure 1. Dynamic pattern of body weight of rats in the modeling of sustained arterial hypertension and after modeling and administration of the oxazole derivative at the dose of 25 mg/kg.

Table 1. Dynamic pattern of mean arterial pressure of rats in the modeling of sustained arterial hypertension and after administration of the 1.3-oxazole-4-il-phosphonic acid derivative.

Groups of animals	Mean arterial pressure (mm Hg)			
	Baseline value	On the 21st day of AH modeling	On the 1st day after test compound administration	On the 7th day after test compound administration
Group No. 1	89.3 ± 2.7	89.25 ± 1.8	-	-
% of change		-0.05[1]		
Group No. 2	90.2 ± 2.3	-	91.5 ± 2.1	93.3 ± 2.5
% of change			+1.4[1]	+3.4[1]
Group No. 3	84.5 ± 2.1	105.3 ± 2.1*	-	-
% of change		+24.6[1]		
Group No. 4	88.1 ± 2.6	104.8 ± 1.7*	76.5 ± 1.7*#^	84.5 ± 2.1#^
% of change		+19.0[1]	-13.2[1] -27.0[2]	-4.1[1] -19.4[2]
Group No. 5	95.5 ± 1.1	116.7 ± 1.4*	89.7 ± 2.1#	96.2 ± 1.2#
% of change		+22.2[1]	-6.1[1] -23.1[2]	+0.7[1] -17.6[2]

Note: *: P < 0.05 relative to the baseline value, #: P < 0.05 relative to the value on the 21st day in the modeling of AH; ^: P < 0.05 relative to the value in group No. 5 on the relevant study day; [1]: % of changes relative to the baseline value; [2]: % of changes relative to the value on the 21st day in the modeling of AH.

Table 2. Dynamic pattern of heart rate of rats in the modeling of sustained arterial hypertension and after administration of 1.3-oxazole-4-il-phosphonic acid derivative.

Groups of animals	Heart rate (bpm)			
	Baseline value	On the 21st day of AH modeling	On the 1st day after test compound administration	On the 7th day after test compound administration
Group No. 1	369.6 ± 6.4	370.0 ± 5.7	-	-
% of change		+0.1[1]		
Group No. 2	365.4 ± 5.3	-	367.8 ± 5.5	409.2 ± 9.2*
% of change			+0.7	+12.0[1]
Group No. 3	365.4 ± 12.5	385.0 ± 7.6	-	-
% of change		+5.4[1]		
Group No. 4	363.3 ± 4.8	377.5 ± 9.7	369.2 ± 9.2	356.4 ± 8.8
% of change		+3.9[1]	+1.6[1] -2.2[2]	-1.9[1] -5.6[2]
Group No. 5	370.7 ± 4.1	365.1 ± 3.9	359.4 ± 4.0	350.8 ± 2.4
% of change		-1.5[1]	-3.0[1] -1.6[2]	-5.4[1] -3.9[2]

Note: *: P < 0.05 relative to the baseline value; [1]: % of changes related to the baseline value; [2]: % of changes relative to the value on the 21st day in the modeling of AH.

groups No. 4 and 5, MAP continued to decrease almost in a similar manner in both groups, by 19.4% ($P < 0.05$) and 17.6% ($P < 0.05$), respectively relative to the data, which were recorded in animals with AH. In this case, heart rate in both groups remained practically unchanged. Thus, for a treatment regimen of 7 days, intraperitoneal administration of the 1.3-oxazole-4-il-phosphonic acid derivative at the dose of 25 mg/kg shows a pronounced hypotensive effect. The latent period of the test compound is 30-40 minutes. The hypotensive effect of the oxazole derivative is comparable to the effect of amlodipine, the test compound being non-toxic unlike amlodipine, since the LD_{50} of oxazole derivative is 5 times higher than amlodipine [5, 11].

In group No. 6, 14 days after the initiation of salt load, an increase in MAP by 13.3% ($P < 0.05$) relative to the baseline value as well as a tendency towards increase in heart rate was observed. The oxazole derivative with daily administration for 7 days resulted in a significant decrease in MAP, practically to the baseline value, relative to the data recorded not only on the 21st day (the term of the induced AH), but also on the 14th day from the initiation of salt load. In addition, heart rate in this regimen of administration of the compound practically did not differ from the baseline level. Thus, under conditions of salt load, the test compound prevents the formation of AH. The oxazole derivative administered for 7 days against a background of elevated MAP shows the hypotensive effect and normalizes heart rate.

CONCLUSION

1. On intraperitoneal administration of the 1.3-oxazole-4-il-phosphonic acid derivative at the dose of 25 mg/kg for 7 days in normotensive unanesthetized rats, mean arterial pressure remains practically unchanged, with the heart rate rising by 12.0% on the 7th day ($P < 0$ .05), which could be due to the inclusion of compensatory mechanisms for the cardiovascular system regulation.
2. In the treatment regimen of single intraperitoneal administration of 25 mg/kg oxazole derivative to the rats with saline-induced arterial hypertension for 7 days, the studied compound showed a pronounced hypotensive effect. The latent period of the test substance is 30-40 minutes. On the first day after administration of the oxazole derivative, the mean arterial pressure decreased by 27.0% ($P < 0.05$), and on the 7th day by 19.4% ($P < 0.05$) relative to the data recorded in animals with arterial hypertension. The hypotensive effect of the oxazole derivative is comparable to the effect of amlodipine, the test compound being non-toxic unlike amlodipine, since the LD_{50} of the oxazole derivative is 5 times higher than amlodipine.
3. In conditions of salt load, the test compound prevents the formation of arterial hypertension. 7-day administration of the oxazole derivative against a background of elevated mean arterial pressure shows a hypotensive effect and normalizes heart rate.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests to declare.

ABBREVIATIONS

AH – arterial hypertension
MAP – mean arterial pressure
HR – heart rate

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