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# Preclinical Study of Derivative of 3-Oxypiridone in Experimental Pre-Eclampsia

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## ABSTRACT

**Introduction:** Currently, preeclampsia remains a serious multisystem complication of pregnancy, leading to disability of children and maternal mortality. One of the leading theories of pathogenesis is the theory of oxidative stress. Accordingly, the search for new drugs with antioxidant and antihypoxic effects is promising for the prevention and treatment of preeclampsia.

**Objective.** To study the efficiency of using of 3-oxypiridine derivatesat correction of functional violations occurring in preeclampsia in the experiment.

**Methods.**The experiment was performed on 140 female white rats of Wistar strain weighing 250-300 g. The studied substances were administered within 7 days from 14 to 21 days of pregnancy.On the 21st day of pregnancy, functional tests and laboratory examination were conducted.
Results. Administration of 3-oxypiridine derivates in animals causes the expressed correction of pathological changes in experimental ADMA-like preeclampsia with the highest effect in a higher dose of the test drug. There was a significant rise in systolic and diastolic blood pressure, respectively, the improvement of microcirculation in the placenta.

**Conclusion.**The results of this study prove the future outlook of the use of 3-oxypiridine derivates for correction of functional changes in preeclampsia and substantiate the reasonability of further research in this direction.

**Keywords:** preeclampsia, 3-oxypiridine, mexidol, endothelial dysfunction, rats, proteinuria, microcirculation

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## INTRODUCTION

Preeclampsiaisa systemic pregnancy-related disease characterized by hypertension, proteinuria, edema (peripheral, or, in some cases, central), and organ dysfunction, including thrombocytopenia and hepatic impairment in late pregnancy. According to various authors, the incidence of preeclampsia is 5–7% of all pregnancies. It can cause maternal and neonatal morbidity and mortality (1). The preeclampsia pathogenesis is multifactorial and not fully studied. The principalpathogenesis links are generalized vasoconstriction, abnormality of blood rheology, thromboendothelial dysfunction, oxidative stress, andDIC syndrome development. Oxidative stress is defined as the "imbalance between oxidizers and antioxidants causing the redox imbalance and molecular damage." Active oxygen forms the most common of which are superoxide, hydrogen peroxide, and hydroxyl radical, participate in the oxidative stress pathogenesis (2 -4).

In general, nitrosative stress mainly includes active forms of nitrogen, such as nitric oxide (•NO) and peroxynitrite (ONOO–). In most studies, lipid peroxidation and oxidative stress are considered the main processes responsible for free radicals generation by a poorly perfused placenta, which causes the adhesion of platelets and leukocytes to vascular endothelium, causing vasoconstriction and the peripheral vascular resistance increase (5). Moreover, the placenta vasoconstriction causes the utero-placental circulation decrease, leading to further release of inflammatory cytokines and anti-angiogenic factors involved in the formation of a vicious cycle in oxidative stress aggravation and the development of vascular endothelial dysfunction (6,7).

With regard of the important role of oxidative stress in preeclampsia, studying the endothelium protective action of agents with high antioxidant activity becomes reasonable. 3-oxypiridine derivatives belong

to the group of such compounds. They show antioxidant and antiradical properties belonging to the group of pyridine carboxylic acids which are very prospective for being studied as cardioprotectors, antihypoxic drugs, and prospective means at extreme conditions (8-13).

Accordingly, the objective of our study is investigating the efficiency of 3-hydroxypyridine derivatives in the correction of morphofunctional disorders occurring in ADMA-like preeclampsia.

## MATERIAL AND METHODS

The experiment was performed on 140 female white rats of Wistar strain weighing 250-300 g. Pregnant rats were divided into 7 groups: 1 group – intact, 2 group – control (introduction L-NAME 25 mg/kg), 3 group - introduction of L-NAME and methyldopa (2x0.043 g/kg), 4 group - L-NAME + Mexidol (2x75mg/kg), 5 group - L-NAME + LHT-21-16 (52 mg/kg), 6 group – L-NAME + LHT-21-16 (260 mg/kg), 7 group - L-NAME + LHT-21-16 (260 mg/kg)+ methyldopa (2x0.043 g/kg).

ADMA-like agent - non-selective NO-synthase blocker of N-nitro-L-arginine methyl ester (L-NAME) was administered intraperitoneally in a dose of 25 mg/kg/daily for seven days (day 14-20 of pregnancy) (14, 15, 16).

The introduction of methyldopa was carried out twice a day at a dosage of 2x0.043 g/kg / day from 14 to 21 days of gestation intragastrically.

The comparison drug Mexidol was also administered twice a day at a dosage of 75 mg / kg intramuscularly from 14 to 21 days of pregnancy.

LHT-21-16 (3-hydroxy-2-ethyl-6-methylpyridinium nicotinate) (52.0 mgkg and 260 mg/kg) was administered intraperitoneally once 30 minutes before L-NAME for 7 days from 14 to 21 day of pregnancy(17).

On the 21$^{st}$ day of pregnancy, a laboratory animal was anesthetized by intraperitoneal injection of chloral hydrate in a dose of 300 мг/kg from body weight, after which, functional tests followed [18-21].

The degree of endothelial dysfunction in experimental animals was assessed by the ratio of endothelium-dependent vasodilation and endothelium-independent vasodilation with the subsequent calculation of coefficient of endothelial dysfunction (CED) (22,23,24).

Microcirculation values were expressed in perfusion units.(PU) (25-29).

## RESULTS

After administration of L-NAME on day 21, pregnant rats demonstrated the statistically significant ($p<0.05$) increase in blood pressure, withSBP 194.9±8.26 mm Hg, DBP 141.4±3.53 mm Hg, while in intact animals, systolic and diastolic blood pressure indicators were 132.3±3.46 mm Hg and 92.40±3.87 mmHg, respectively. In the reference (Mexidol) group of animals, a decrease in systolic and diastolic pressure to 177.0±4.02 mm Hg and 133.2±4.63 mmHg accordingly, was detected, that had no significant difference from the control group. The SBP and DBP data in the group of animals treated with methyldopa, the drug included in the standard therapy for hypertensive conditions in pregnant, were 148.9±4.42 mm Hg and 113.6±3.47 mm Hg, which significantly ($p<0.05$) differs from the indicators in the reference group with simulated pathology; however, these figures do not reach the target ones in the group of intact animals. The LHT-21-16 introduction also led to the significant ($p<0.05$) SBP decrease up to 168.4±2.8 mm Hg (at a dose of 52 mg/kg) and 158.3±3.4 mm Hg (260 mg/kg). AfterLHT-21-16 introduction, DBP was 127.9±5.8 mm Hg and 116.3±4.7 mmHg respectively. It can beseen that the hypotensive effect in a larger dose of the test compound approaches to the value in the methyldopa group. The combination of LHT-21-16 (260mg/kg) and methyldopa demonstrated the best results among the studied drugs: SBP and DBP indicators were 142.1±4.2 mm Hg. and 98.5±5.6 mm Hg, not significantly differing from the values in the intact animals group (Table 1).

Introduction of L-NAME to pregnant rats caused theimpairment of the vascular tone regulation mechanisms, as proved by EDCincrease from 1.20±0.07 to 2.93±0.25. The introduction of Mexidol and methyldopa significantly reduced EDC - to 2.31±0.12 and 2.28±0.16, respectively; however, these values did not reach the targetones. In groups of animals with the introduction of the test 3-oxypiridine derivative at doses of 52 mg/kg and 260 mg/kg, a significant EDC decrease was detected to 2.21±0.17 and 1.82±0.24, respectively. The course introduction of the combination LHT-21-16 (260 mg/kg) + methyldopa to pregnant animals with ADMA-like preeclampsia reduced EDC to 1.47±0.15, which is close to the values of the intact group of animals and provesthe expressed endothelial function improvement.

Animals with ADMA-like preeclampsia demonstratedthe microcirculation decrease from 465.9±28.79 PU to 219.8±7.79 PU. Administration of LHT-21-16 compounds in test doses recovered microcirculation to 309.3±7.05 PU and 361.2±9.29 PU, respectively, with lower and higher dosages. These values exceed the results of microcirculation correction with methyldopa and mexidol, for which these values were 296.9±15.36 and 273.8±9.67 PU. However, the best results of microcirculation correction were obtained in the group of animals with the combined administration of a higher dose of LHT-21-16 and methyldopa, after the course drug administration, the microcirculation values amounted to 419.3±8.26 PU.

**Table 1: The impact of 3-oxypiridine derivates on BP, CED and microcirculation in the placenta at ADMA-like preeclampsia**

| Group | SBP (mmHg | DBP(mmHg) | CED (conv.) | Microcirculation (PU) |
|---|---|---|---|---|
| Intact | 132.3±3.46$^{y}$ | 92.4±3.87$^{y}$ | 1.2±0.07$^{y}$ | 465.9±28.79$^{y}$ |
| L-NAME | 194.9±8.26$^{*}$ | 141.4±3.53$^{*}$ | 2.93±0.25$^{*}$ | 219.8±7.79$^{*}$ |
| Methyldopa (2x0.043 g/kg) | 148.9±4.42$^{y*}$ | 113.6±3.47$^{y*}$ | 2.28±0.16$^{y*}$ | 296.9±15.36$^{y*}$ |
| Mexidol (2x75mg/kg) | 177.0±4.02$^{*}$ | 133.2±4.63$^{*}$ | 2.31±0.12$^{y*}$ | 273.8±9.67$^{y*}$ |
| LHT-21-16 (52 mg/kg) | 168.4±2.8$^{y*}$ | 127.9±5.8$^{y*}$ | 2.2±0.2$^{y*}$ | 309.3±7.05$^{y*}$ |
| LHT-21-16 (260 mg/kg) | 158.3±3.4$^{y*}$ | 116.3±4.7$^{y*}$ | 1.8±0.2$^{y*}$ | 361.2±9.29$^{y*}$ |
| LHT-21-16 (260 mg/kg) + Methyldopa (2x0.043 g/kg) | 142.1±4.2$^{y}$ | 98.5±5.6$^{y}$ | 1.5±0.1$^{y}$ | 419.3±8.26$^{y}$ |

Note: From this point on - SBP, DBP – systolic and diastolic blood pressure (mm Hg); CED – the coefficient of endothelial dysfunction (conv.); PU – perfusion units; *- p< 0,05 compared to the group of intact animals; y – p< 0,05 compared to the control group.

## DISCUSSION

The shift of the physiological equilibrium between NO and O2 towards the latter often causes the formation of highly toxic peroxynitrite (ONOO-), causing the membrane damage and favoring the development of inflammatory processes and other impairments (30-34). The main presumptivemechanism of antioxidant action of 3-oxypiridine derivatives is their interaction with peroxy- (ROO-) and alkoxy-radicals (RO-) formed in the course of LPO due to the easily mobile hydrogen of the phenolic group in the molecule. By binding free radicals of reactive oxygen forms, they inhibit LPO processes, that was confirmed in our experiments by the increase of the share of NO metabolites in plasma, improve the endothelium vasodilatory function, and reduce the endothelial dysfunction development (35–37).

## CONFLICT OF INTEREST

None

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