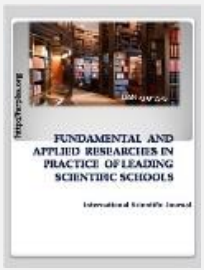

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Morphofunctional parameters of bone marrow of mice under using of antihypertensive agent

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Due to the increase in cardiovascular disease, it is urgent to research new more effective and safe drugs and their combinations. Candesartan cilexetil is an angiotensin II receptor antagonist. It is known that candesartan cilexetil has a number of side effects, affecting the antioxidant system. Therefore, we studied the natural antioxidant resveratrol to prevent the cytotoxic effect. Goal. To study the effect of candesartan cilexetil and resveratrol in different doses on the number of apoptotic and micronucleated cells and cell cycle parameters in mice. Methods. Male C57Bl/6 mice were used for the experiment. Animals were received intragastrically candesartan cilexetil and resveratrol in different doses for 7 weeks. Evaluation of the effects of substances on cytogenetic and cytokinetic parameters of bone marrow was conducted by flow cytometry. Results. It was found that candesartan cilexetil at 1.5 mg/kg dose was cytotoxic. Using candesartan with resveratrol was safer for cells of bone marrow. Natural resveratrol reduced in combination the adverse effects of candesartan cilexetil. Test complex of substances stimulated cell proliferation in bone marrow of mice. Conclusions. New combination of candesartan cilexetil and resveratrol increased proliferation of cells and was not cytotoxic.

Keywords. *Candesartan cilexetil; resveratrol; apoptotic cells; micronuclei; cell cycle parameters.*

Introduction

Due to the increase in cardiovascular disease, it is urgent to research new more effective and safe drugs and create their combinations. Candesartan cilexetil is an angiotensin II receptor antagonist. [1]. Candesartan cilexetil increases resistance to stress and endurance during exercise in people with hypertension [2].

Resveratrol is a natural polyphenol. It shows pleiotropic health beneficial effects, including anti-oxidant, anti-inflammatory, anti-aging, cardioprotective and neuroprotective activities [3-5]. It's known that this substance decreases the synthesis of lipids in liver and eicosanoids in leukocytes in animals, inhibits platelet activation/aggregation, decreases the activity of protein kinases, inhibits formation of reactive oxygen species [6].

The aim of current study is investigation of the effect of candesartan cilexetil, resveratrol and their combination on cytogenetic and cytokinetic parameters *in vivo* using mice.

Materials and methods

Male C57Bl/6 mice were used in the experiment. Animals were divided into 6 groups. Mice of each group received investigated substances intragastrally at different dosages for 7 weeks: group 1 of animals were given candesartan cilexetil at 1.5 mg/kg dose (average therapeutic dose for treatment of hypertension according to the instruction), mice of group 2 received resveratrol at 1 mg/kg dose; group 3 of animals were given resveratrol at 10 mg/kg dose, group 4 of mice was administrated candesartan cilexetil at 1.5 mg/kg dose and resveratrol at 1 mg/kg dose; group 5 of animals received candesartan cilexetil at 1.5 mg/kg dose and resveratrol at 10 mg/kg dose, control mice were given an intragastrally 1% starch solution.

The administered doses of the studied substances were calculated using the interspecific conversion formula: [7]:

$$A = \frac{B \times \kappa(B)}{\kappa(A)}$$

A – required dose;
B – known dose;
κ (B) – conversion factor for weight B;
κ (A) – conversion factor for weight A.

The ratio of apoptotic cells, the number of micronucleated cells and parameters of cell cycle were checked using flow cytometry method.

The results are presented as mean±SEM. We used Student's t-test to compare 2 samples and one-way ANOVA for multiple comparisons followed by pair-wise comparison.

Results and discussion

The effect of using of candesartan cilexetil, resveratrol and their combination on cytogenetics and cytokinetic parameters in mice was studied. At first the number of apoptotic cells was investigated. The obtained data are presented in Figure 1. It was shown that candesartan cilexetil at 1.5 mg/kg dose increased the ratio of apoptotic cells in bone marrow of C57Bl/6 mice as compared to the control. Resveratrol at 1 mg/kg, 10 mg/kg doses and the combination of candesartan cilexetil at 1.5 mg/kg dose with resveratrol at 1 mg/kg dose significant decreased the count of cells with damage of genetic material. The number of apoptotic cells was less in group 4 of animals. This is evidence that natural resveratrol decreases side effects of candesartan cilexetil on cells (Figure 1).

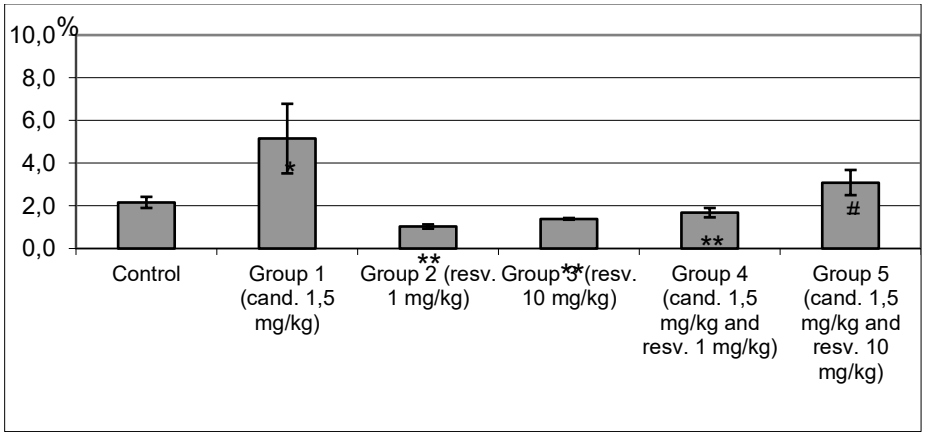

Fig 1. The number of apoptotic cells in bone marrow of C57Bl/6 mice under using candesartan cilexetil and resveratrol.

cand. – candesartan cilexetil; resv. – resveratrol; * – in comparison with the control ($p<0.05$); ** – in comparison with group 1 ($p<0.05$); # – in comparison with group 2 ($p<0.05$).

It was recorded that studied substances influence the number of cells with micronuclei (Figure 1).

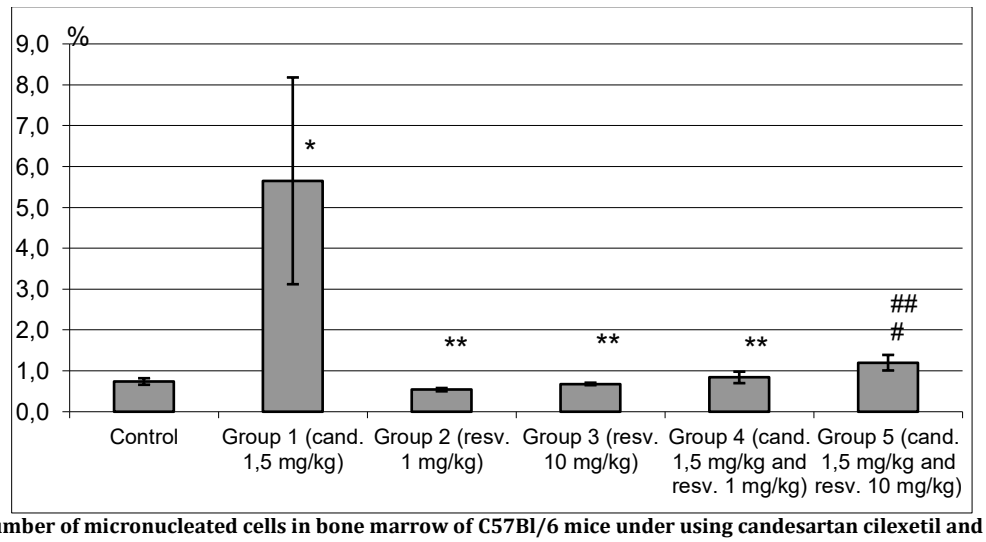

Fig 2. The number of micronucleated cells in bone marrow of C57Bl/6 mice under using candesartan cilexetil and resveratrol.

cand. – candesartan cilexetil; resv. – resveratrol; * – in comparison with the control ($p<0.05$); ** – in comparison with group 1 ($p<0.05$); # – in comparison with group 2 ($p<0.05$); ## – in comparison with group 3 ($p<0.05$).

Candesartan cilexetil at 1.5 mg/kg dose increased the ratio of micrinucleated cells in bone marrow as compared to the control ($p<0.05$). The number of cells with micronuclei was less under using resveratrol at 1 mg/kg and 10 mg/kg doses and the combination of candesartan cilexetil at 1.5 mg/kg dose with resveratrol at 1 mg/kg dose ($p<0.05$).

The results of investigation of parameters of cell cycle are presented in Figure 3.

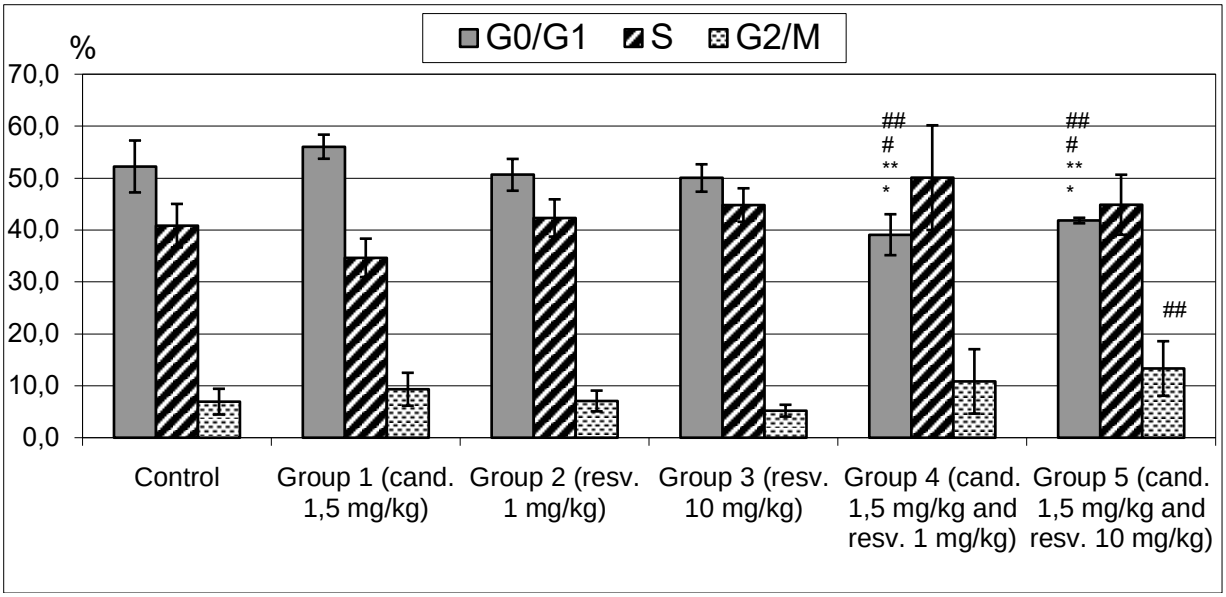

Fig 3. Distribution of cells at phases of cell cycle in bone marrow of C57Bl/6 mice under using candesartan cilexetil and resveratrol.

cand. – candesartan cilexetil; resv. – resveratrol; * – in comparison with the control ($p<0.05$); ** – in comparison with group 1 ($p<0.05$); # – in comparison with group 2 ($p<0.05$); ## – in comparison with group 3 ($p<0.05$).

It was shown that new combination of candesartan cilexetil at 1.5 mg/kg dose and resveratrol at 1 mg/kg stimulated cell proliferation in bone marrow of C57Bl/6 mice as compared to the control and using studied substances alone. Combination of candesartan cilexetil at 1.5 mg/kg dose with resveratrol at 1 mg/kg and combination of candesartan cilexetil at 1.5 mg/kg dose with resveratrol at 10 mg/kg decreased the amount of cells at G_0/G_1 stage (Figure 3).

Some authors found that candesartan cilexetil has several side effects. High doses of candesartan cilexetil influence the formation of separate subpopulations of cells in bone marrow [8]. G. Mantzios et al. showed that candesartan cilexetil was cause of autoimmune haemolytic anaemia [9].

Conclusions

It was found that new combination of substances such as candesartan cilexetil and resveratrol was safe for cells of bone marrow of animals. Using candesartan cilexetil led to the formation apoptotic cells and micrinucleated cells. Antioxidant resveratrol decreased cytotoxic effect of candesartan cilexetil. It was shown that application candesartan cilexetil with resveratrol stimulated cell proliferation. The obtained results are important to develop new complex drug to treat cardiovascular diseases, which is safe and effective in stimulation of cell proliferation.

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