World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 1, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

SHORT AND LONG-TERM USE OF CANDESARTAN AND RAMIPRIL IN SPONTANEOUSLY HYPERTENSIVE RATS, LIVER, KIDNEY AND HEART MORPHOLOGY

Maruschak A.V. *

Assistant of the Pathological Physiology, Department of Higher State Educational Institution of Ukraine, Bukovinian State Medical University, UKRAINE.

Received on: 08-01-2019; Revised and Accepted on: 29-01-2019

ABSTRACT

Resume: *Choosing a method of treating arterial hypertension remains an urgent problem today. For effective therapy, it is necessary to select hypotensive drugs that not only effectively reduce the pressure, but also contribute to the restoration of the structure of tissues sensitive to oscillations of arterial pressure.*

Purpose: *The purpose of this study was to conduct a comparative analysis of the effect of angiotensin 2-candesartan receptor antagonist and angiotensin converting factor ramipril on pathomorphological changes in the myocardium, kidney, and liver in SHR lines that received treatment for 7 days (short) and 21 days (prolonged therapy)*

Materials and Methods: *The study was conducted on 20 spontaneously hypertensive rats with a mass of 248.0-441.0 g. The rabbit was administered at a dose of 5 mg / kg and candesartan 4 mg / kg, respectively. The period of short-term therapy was 7 days and long-term-21 days. For the evaluation of morphological changes in the heart, kidneys, liver, frozen cross sections were stained using Ramonovsky-Giemsa method.*

Research Results: *The data obtained indicate a more significant effect of candesartan on myocardium and kidney. Ramipril had a negative effect on the renal tubules, increasing the degree of atrophy. Treatment with ramipril and candesartan, especially with long-term use, reduced the hydrophilic swelling of hepatocytes.*

KEYWORDS: *Candesartan, Ramipril, Hypertensive Rats, Liver, Kidney and Heart Morphology.*

INTRODUCTION

Hypertension is one of the essential problems all over the world. Approximately half of the all death-cases caused by cardio-vascular diseases are connected with hypertension and also with it's illnesses and complication such as stroke. Coronary heart disease heart failure, reduction of the blood pressure to normal level is the main factor of prevention from cardio-vascular diseases. When treating hypertension one should use not only those medicines when have drastic impact on hypertension, but also those when can renew the structure of the tissues which are vulnerable to changes in blood pressure. However the influence on morphology of cardiac muscle, kidneys and liver is not studied enough.

***Corresponding author:**

Maruschak A.V.

Assistant of the Pathological Physiology,

Department of Higher State Educational Institution of Ukraine,

Bukovinian State Medical University, UKRAINE.

** E-Mail: alionka5505@gmail.com*

DOI: https://doi.org/10.5281/zenodo.2555307

METHODOLOGY

The research was done due to 20 spontaneously hypertensive rats with weight of 248, 0 – 431, 0 h (breeding-gram of laboratory animals "Biomodel-service", Kiev).

The animals were kept in vivarium at the temperature of 20-25^{0}C, natural light, in standard plastic cages, fed on standart diet. The group of SHR series were injected the inhibitors of angiotensin connecting enzyme. The dosis of Ramipril 5 mg/kg (Germany) and Candesartan 4 mg/kg (Ranbasy Laboratories Limited) was in conformance with daily doses of the human. Medications which were compared, were green 1 time a day in food throughout the week (sport-term therapy) and throughout 21 days (long-term therapy). The control group of SHR series animals were green 0.9% solution of NaCl in the equivalent volume (0.2 ml/200g) through the stomach. Frozen transverse cuts of the heart, kidneys and liver with thickness of 10 m Romanovsky-Gymza staining with using of hematoxylin and eosin.

For ultra- structural researches one used the method of epoxy staining with preliminary fixation in glutaraldehyde

and osmium tetroxide. Ultra fine cuts were contrasted due to uramyl acetate and lead citrate by Reynolds and studied due to electronic microscope. JEOL 100CX (Japam).

Experimental data and euthanasia were made according to international principles of European Convention for the Protection of Vertebrate Animals (Strasburg, 1985). The processing of result was carried out with using of generally accepted variation statistics methods. Quantity indicatory were due to the test of Kolmogorace – Smirna, deviations from normal data distribution were not observed (p≥0.05). For estimation of statistic indicators one used Student t criterium.

RESULTS AND DISCUSSION

Control group of SHR series animals had atrophy 8,4±0,14% of glomeruli that used expressed in diminution of their series, because of decrease in cells and compact arrangement (fig.1), in other glomeruli one can notice hypertrophy and increase in cells amount (fig.1).

Arteries and arterioles are usually hypertrophied at the expense of increase in leomyocytes with thickened media (fig.2). 24,2 ± 0,22% leomyocytes with signs of hydropic vacuolization (vacuolar dystrophy). The endotheliocytes of these vessels are in condition of desquamation at different stages. The damage to epithelium of convoluted tubules is concluded due to the regions of regeneration with polygonal cells which have dark cytoplasm and dark nuclei (fig.3).

One can observe hypertrophy in the walls of the left ventricle and particularly in intraventricular septum with increase in size of cardiomyocites and deformation of muscle fiber bunches in myocardium of control group of animals. In 14,1±0,19% of cardiomyocites one points out hydropic swelling (granular dystrophy), when in 5,3±0,12% - basophilic degeneration (fig.4).

In liver one observes reverse swelling 94±0,34% of hepatocytes. Under this condition hydropic swelling is observed in central lobe (III zone of acinus), and hydropic vacuolization in I zone acinus (fih.5).

The ramipril treatment (short-term) has lead to the slight reduction in square of atrophy to 8.3±0.18% (fig.1a), hypertrophy of arteries and arterioles walls saved it's tendency and increased under the influence of ramipril to 24.5±0.28% (fig.2a).

Considerable impact on myocardium was made by ramipril throughout short-term treatment. The degree of hydropic swelling has decreased 3,5 times to 4.1±0.10% (fig. 4a), when basophilic degeneration is observed in 0.8±0.04% of cardiomyocytes, that is 6.25 times less than in control group.

Positive impact was made by modification liver, the degree of hydropic swelling of hepatocytes decreased to 93±0.38%, but the indices weren't cogent (fig. 5a).

In group of animals which were treated with Ramipril during 21 days one points out deep atrophy 8.6±0.17% of renal tubules (fig. Ib). The hypertrophy of arteries and arterioles walls decreased significantly to 8.1±0.20% (to 3 times) in comparison with indices of control group of animals (fig. 2b).

Only in 0.9±0.03% of cardiomyocytes one observes basophilic degeneration without signs of hydropic swelling (fig. 4b).

The square of reverse swelling decreased 2.3 times to 42±0.30% in the liver (fig. 5b).

One observes atrophy in kidneys practically at the same level as in the control group 8.2±0.15% under the short term treatment with candesartan (fig. 1v).

The zone of hypertrophy of arteries and arterioles media is considered to be smaller (fig. 2v).

The same results were obtained in myocardiac under the short-term treatment with medication as were obtained due to long-term treatment with ramipril (fig.4v).

The short-term consumption of candesartan had no effect on hydropic swelling of the liver, as the indices had been at the same liver with control group of animals (fig. 5v).

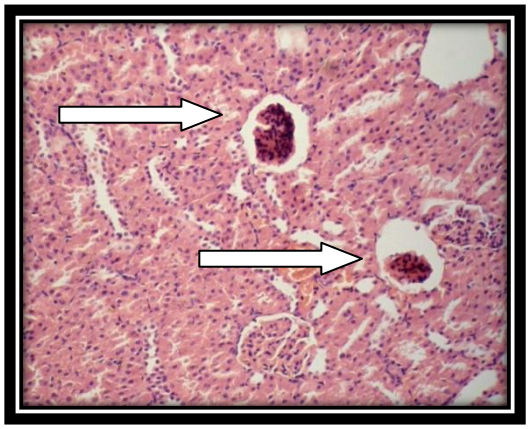

Fig. 1: Cortical substance of the kidney. Control group of SHR series. Arrows indicate atrophied glomeruli, other glomeruli in a state of hypertrophy. Coloring with hematoxylin and eosin. Eye.10^{x}. Lens.10^{x}

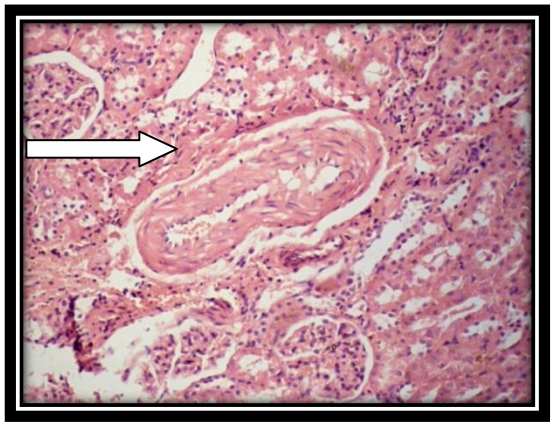

Fig. 2: Cortical substance of the kidney. Control group of SHR series. The arrows indicate the hypertrophied walls of the vessels. Coloring with hematoxylin and eosin. Eye.10^{x}. Lens.10^{x}

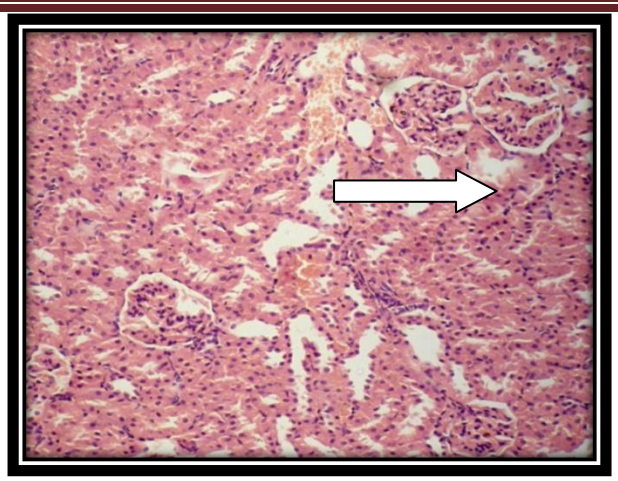

Fig. 3: Cortical substance of the kidney. Control group of SHR series. The arrows indicate incomplete renal tubules. Coloring with hematoxylin and eosin. Eye.10^{x}. Lens.10^{x}

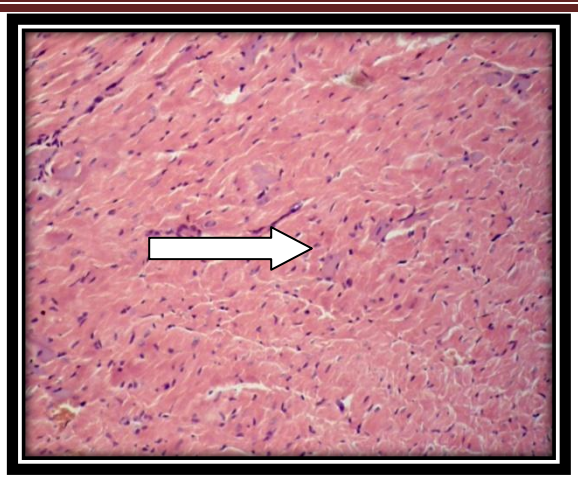

Fig. 4: Myocardial ventricles of the rat. Control group of SHR series. Arrows indicate hypertrophy of the wall. Coloring with hematoxylin and eosin. Eye.10^{x}. Lens.10^{x}

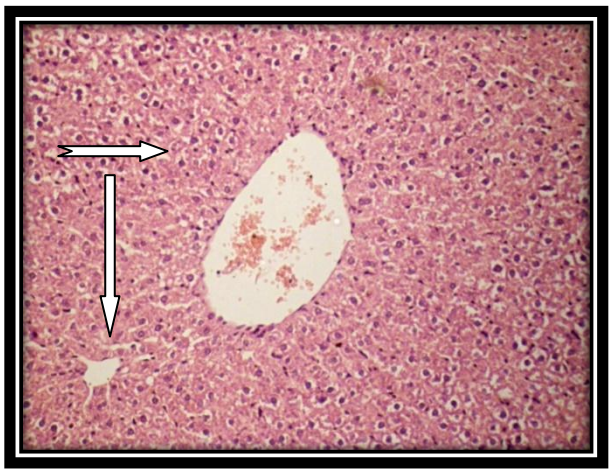

Fig. 5: Rat's liver. Control group of SHR series. The arrows indicate the hydropic swelling of hepatocytes and hydro-oven vacuolation. Coloring with hematoxylin and eosin. Eye.10^{x}. Lens.10^{x}

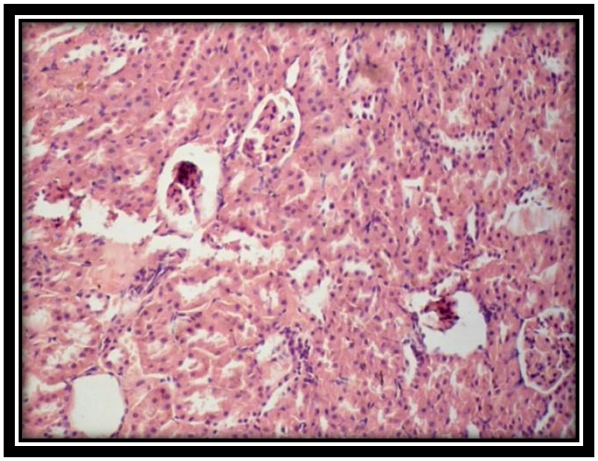

Fig. 1a: Cortical substance of the kidney. Ramipril treatment (short-term) group of SHR series. Arrows indicate atrophied glomeruli, other glomeruli in a state of hypertrophy. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

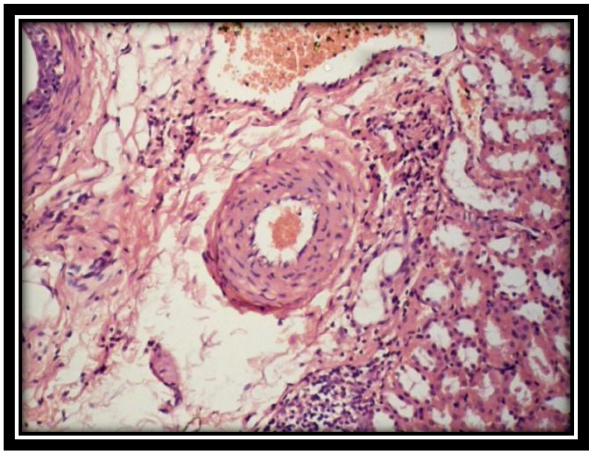

Fig. 2a: Cortical substance of the kidney. Ramipril treatment (short-term) group of SHR series. The arrows indicate the hypertrophied walls of the vessels. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

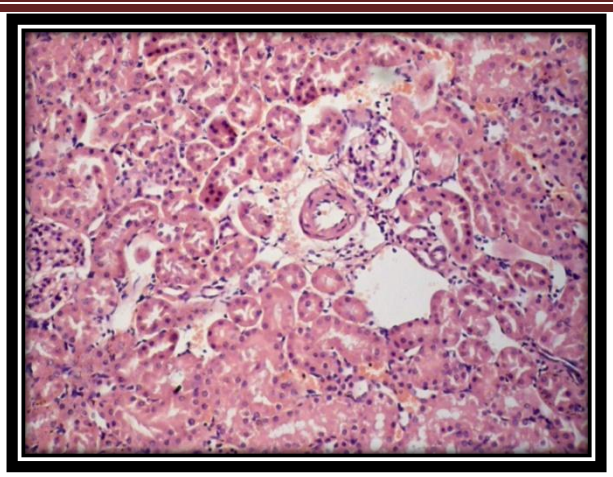

Fig. 3a: Cortical substance of the kidney. Ramipril treatment (short-term) group of SHR series. The arrows indicate incomplete renal tubules. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

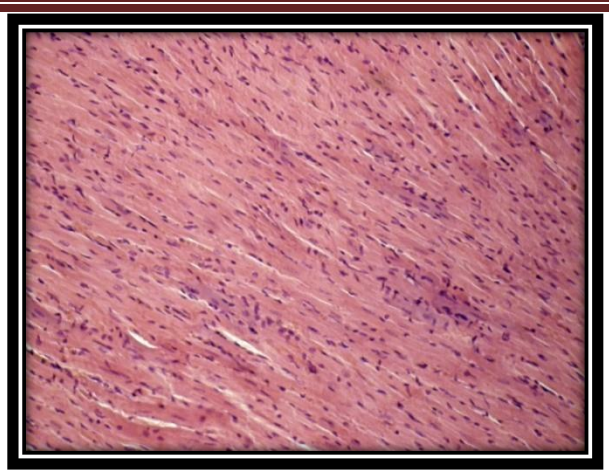

Fig. 4a: Myocardial ventricles of the rat. Ramipril treatment (short-term) group of SHR series. Arrows indicate hypertrophy of the wall. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

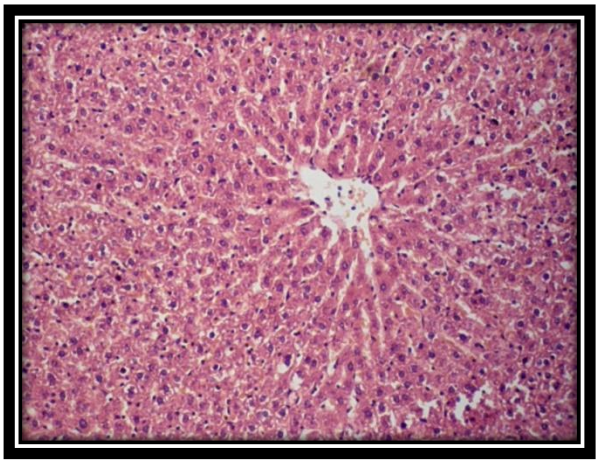

Fig. 5a: Rat's liver. Ramiptil treatment (short-term) group of SHR series. The arrows indicate the hydropic swelling of hepatocytes and hydro-oven vacuolation. Coloring with hematoxylin and eosin. Eye.10^x. Lens.10^x

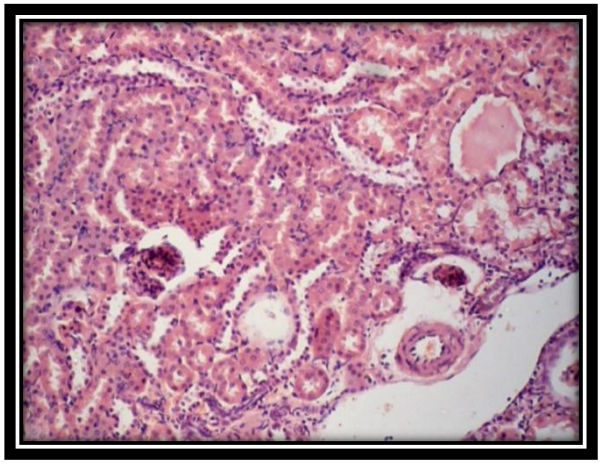

Fig. 1b: Cortical substance of the kidney. Ramipril treatment (longt-term) group of SHR series. Arrows indicate atrophied glomeruli, other glomeruli in a state of hypertrophy. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

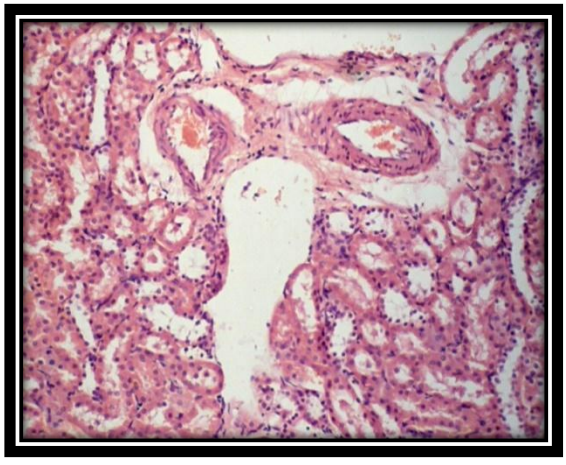

Fig. 2b: Cortical substance of the kidney. Ramipril treatment (longt-term) group of SHR series. The arrows indicate the hypertrophied walls of the vessels. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

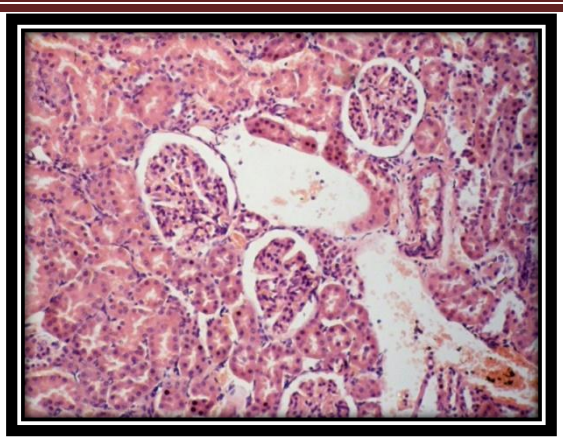

Fig. 3b: Cortical substance of the kidney. Ramipril treatment (long-term) group of SHR series. The arrows indicate incomplete renal tubules. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

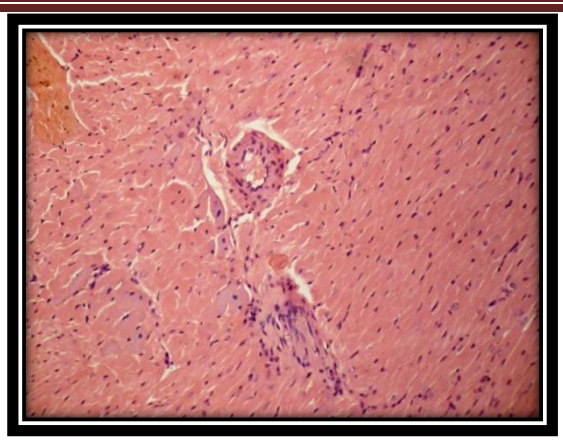

Fig. 4b: Myocardial ventricles of the rat. Ramipril treatment (long-term) group of SHR series. Arrows indicate hypertrophy of the wall. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

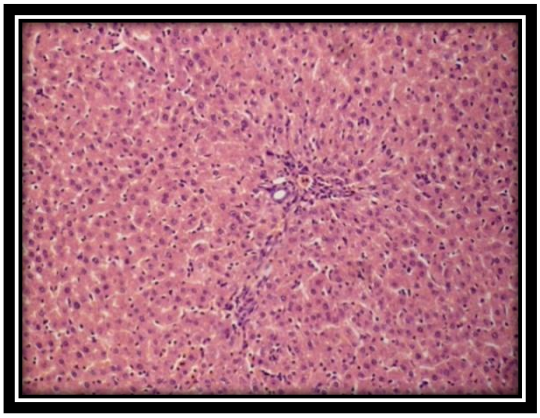

Fig. 5b: Rat's liver. Ramiptil treatment (long-term) group of SHR series. The arrows indicate the hydropic swelling of hepatocytes and hydro-oven vacuolation. Coloring with hematoxylin and eosin. Eye.10^x. Lens.10^x

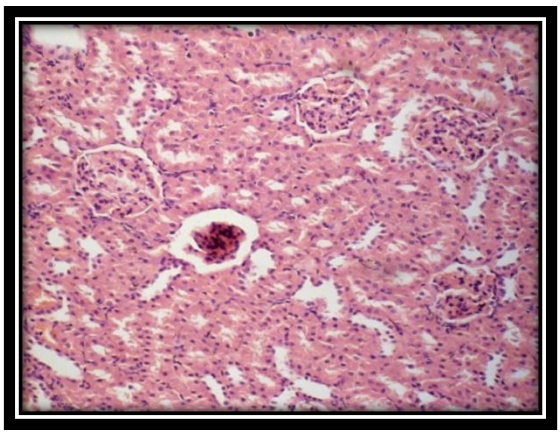

Fig. 1v: Cortical substance of the kidney. Candesartan treatment (short-term) group of SHR series. Arrows indicate atrophied glomeruli, other glomeruli in a state of hypertrophy. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

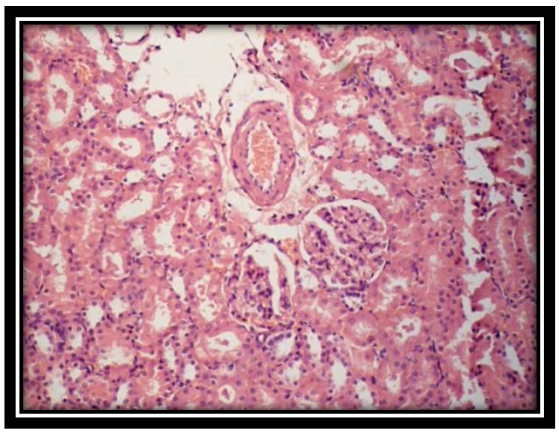

Fig. 2v: Cortical substance of the kidney. Candesartan treatment (short-term) group of SHR series. The arrows indicate the hypertrophied walls of the vessels. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

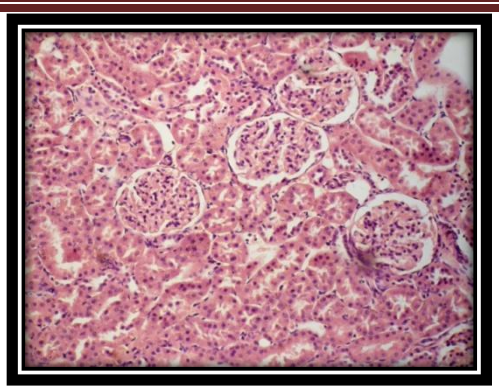

Fig. 3v: Cortical substance of the kidney. Candesartan treatment (short-term) group of SHR series. The arrows indicate incomplete renal tubules. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

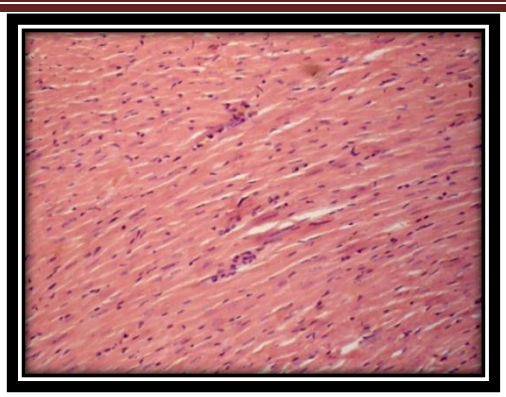

Fig. 4v: Myocardial ventricles of the rat. Candesartan treatment (short-term) group of SHR series. Arrows indicate hypertrophy of the wall. Coloring with hematoxylin and eosin. Eye.10x. Lens.10x

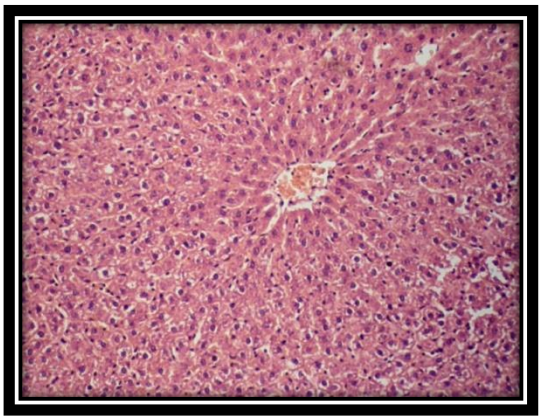

Fig. 5v: Rat's liver. Candesartan treatment (short-term) group of SHR series.The arrows indicate the hydropic swelling of hepatocytes and hydro-oven vacuolation. Coloring with hematoxylin and eosin. Eye.10^x. Lens.10^x

The long-term treatment with candesartan didn't reduce the degree of renal tubules atrophy, but greatly influenced the degree of arteries and arterioles walls (fig. 2g). According to the literature losartan and ramipril provided effective BP control and demonstrated that despite the increase in renal volume, losartan and ramipril may have regressed renal progression via other factors. These two groups of antihypertensive drugs may also have beneficial effects on the retardation of renal progression.

CONCLUSION

Candesartan had a more significant effect on the myocardium compared with ramipril, and contributed to a decrease in basophilic degeneration and the disappearance of hydrocardic swelling of cardiomyocytes.

Significant changes in the kidneys caused the use of ramipril and for a long and short-term use, and they were of a negative nature. This marked a deeper atrophy of the renal tubules, but the hypertrophy of the walls of the arteries and arterioles decreased significantly.

The effect of candesartan on the kidneys was more effective, but there was no complete restoration to the level of control animals.

Significant was the effect of ramipril on the liver, there was a decrease in the degree of reverse swelling of hepatocytes, but the use of candesartan produced a stronger effect.

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How to cite this article:

Maruschak A.V. SHORT AND LONG-TERM USE OF CANDESARTAN AND RAMIPRIL IN SPONTANEOUSLY HYPERTENSIVE RATS, LIVER, KIDNEY AND HEART MORPHOLOGY. J Pharm Res 2019;8(1):15-21. **DOI: https://doi.org/10.5281/zenodo.2555307**

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil