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Activity of Lysosomal Enzymes During Triple Combination Antihypertensive Treatment of Arterial Hypertension

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Abstract: *Summary:* The aim of the study has been to study the biochemical parameters of blood, the activity of lysosomal enzymes in models of arterial hypertension (AH) and assess the effectiveness of three-component antihypertensive treatment. *Research materials and methods:* The experiment has included 23 rabbits of Chinchilla breed weighing 2.5-3.0kg, which the AH model has been created in. Of these, 8 rabbits which have not received antihypertensive therapy (AHT) have made up the control group. After 4 weeks of model creation, AHT has been started in 15 rabbits of the main group within 1 month. Over the course of 8 weeks, systolic blood pressure (SBP) and diastolic blood pressure (DBP) have been measured in rabbits using a veterinary electronic tonometer. Along with this, the level of creatinine, urea, residual nitrogen in the blood plasma, the activity of the enzymes lactate dehydrogenase (LDH) and the MB fraction of creatine phosphokinase (CPK-MB) have been determined, ECG studies have been performed. All rabbits have been prescribed valsartan/amlodipine/hydrochlorthiazide (80/12.5/5mg and 160/25/10mg), choosing an individual dose depending on blood pressure once a day per os. *Results*: During the study, along with an increase in blood pressure, an increase in the level of creatinine, residual nitrogen and urine in the blood plasma has been revealed when creating a model of hypertension, which has been accompanied by an increase during the month. A decrease in the activity of the enzyme LDH and CPK-MB has been also noted. After the therapy hold for 1 month, positive dynamics have been found both in the level of blood pressure and indicators of biochemical analysis. Since creatinine concentration has decreased by 28.5%, residual nitrogen – by 36%, urea – by 40%, LDH activity has increased by 30%, CPK-MB by 40%. *Conclusion:* Thus, along with an increase in blood pressure and indicators of biochemical analysis, a decrease in the activity of lysosomal enzymes is noted in AP models. An increase in the activity of the enzymes LDH and CPK-MB during the three-component AHT shows that the components of this combination affect various parts of the cellular metabolism.

Keywords: Experimental Models, Arterial Hypertension, Lysosomal Enzymes, Fixed Drug Combination

1. Introduction

Despite the achievements of modern medicine, the problem of arterial hypertension (AH) is still one of the issues on the agenda. AH is a widespread non-infectious disease and is of great importance as a major risk factor in the development of stroke, myocardial infarction and cardiac death. In order to study the causes of blood pressure (BP) dysregulation, more deeply various Ah models are used on animals [1-3]. Considering that the kidneys play an important role in maintaining the hemodynamic balance and in the development of changes in the level of BP, the study of nephrogenic form of AH models is of great importance when clarifying the reasons why BP remains at a high level. During the modeling of AH in the experiment, the method proposed by H. Goldblatt (1934, 1939) in the last century is used [4, 5]. The AH model on experimental kidney developed by H. Goldblatt had a special role in studying the development mechanisms of not only symptomatic but also essential hypertension. H. Goldblatt believed that BP in the experimental animals observed by him was caused by the decrease in the main renal blood circulation as a result of the development of kidney ischemia during the compression of the renal artery and the increase in the concentration of renin in the blood [6-8].

Taking all of these into account our goal was to study

biochemical indicators, the activity of lysosomal enzymes in the blood and to evaluate the effectiveness of the fixed triple antihypertensive treatment by creating BP model on rabbits.

2. Material and Treatment Methods

In the experiment, 23 Chinchilla rabbits weighing 2.5-3.0 kg were used and the BP model was created. The experiment lasted for 8 weeks. 8 rabbits included in the experiment did not receive antihypertensive treatment and formed the comparison group. 15 rabbits formed the main group. 4 weeks after the model was createdthe effectiveness of antihypertensive treatment in them has been studied within 1 month. In order to create the AH model, the method proposed by Goldblatt H. and KAPn J. (1938), based on the compression of the abdominal aorta on the area where the renal arteries are separated, was used [9-11]. This method is less damaging and allows for higher and more stable BP. Maximal (SBP) and minimal AH (DBP) were determined on the models over a period of 8 weeks using a CONTEC08A-VET veterinary electronic tonometer on the upper arm or thigh (sometimes from the tail). At the same time, biochemical analysis of blood was performed in all rabbits - concentration of creatinine, urea, residual nitrogen in plasma was determined, the activity of lactate dehydrogenase (LDH) and creatine phosphokinase-MB fraction (CPK-MB) enzymes was studied using the traditional method in the MS BioScreen-500 biochemical analyzer with reagents from the German company "HUMAN". In addition to laboratory examinations, electrocardiography (ECG) examination was performed with a 3-channel "HeartScreen 60G" electrocardiograph belonging to the Hungarian Innomed company.

Hypotensive treatment was started for the participants of the experiment 4 weeks after the modeling operation. The dose of valsartan/amlodipine/hydrochlorthiazide preparation (80/12, 5/5 – 160/25/10 mg) was selected according to the level of AH and was given per os once a day to all rabbits.

In order to compare the quantitative indicators in the groups, a non-parametric method that evaluates the difference between the indicators - Mann-Whitney's U criterion was used. At this time, the statistical difference between groups was considered fair when indicated $p<0,05$. The statistical processing of the obtained results was carried out using modern software equipment - Microsoft Excel spreadsheet editor and IBM SPSS Statistics statistical computer program for processing the results.

3. Conclusions and Discussion

During AH monitoring, at the beginning of the study, SBP was 120,2 ± 2,5 mmHg and DBP was 90,0 ± 1,7 mmHg in all rabbits. During the biochemical analysis of blood, the concentration of creatinine was at the level of 88,4 ± 9,3 mkmol/l, residual nitrogen was 25,5 ± 1,7mmol/l, and urea was 8,6 ± 0,6 mmol/l on average. At this time, the activity of LDH enzyme was at the level of 422,1 ± 44,2 U/l U/l and CPK-MB was 563,2 ± 41,2 U/l.

On the 15th day after the creation of the AH model, the concentration of creatinine in the blood was 93,9 ± 8,0 mkmol/l, residual nitrogen was – 31,8 ± 3,7 mmol/l, and urea was - 11,0 ± 1,8 mmol/l. The activity of LDH was 372,4 ± 18,1 U/l, and CPK-MB was 415,6 ± 36,2 U/l. At this time, only the level of CPK-MB enzyme differed with statistical integrity ($p < 0,05$).

In ligatured rabbits SBP increased up to 140,3 ± 4,3 mmHg, and DBP increased to 100,7 ± 2,1 mmHgboth directly due to the activation of the renin-angiotensin system and the increase in the formation of angiotensin II and by raising peripheral vascular resistance indirectlyincreasing the activity of the sympathetic nervous system and the level of catecholamines.

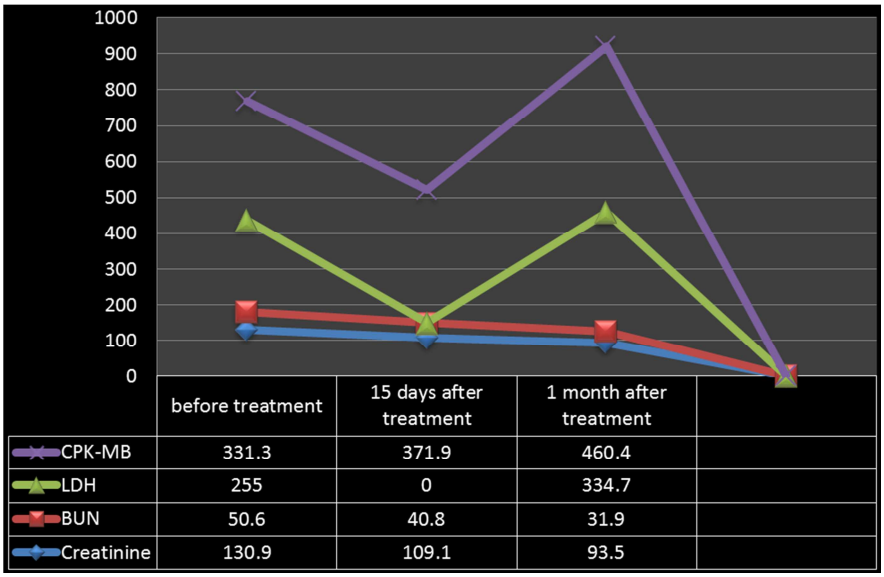
A statistically significant difference was found in all indicators 1 month after the creation of the model. At this time, creatinine concentration was 130,9 ± 8,0 mkmol/l ($p < 0,01$), residual nitrogen was - 50,6 ± 1,6 mmol/l ($p < 0,001$), and ureawas - 20,3 ± 0,8 mmol/l ($p < 0,001$). The activity of LDH decreased to 255,0±14,1 U/l ($p < 0,05$) and CPK-MB to - 331,3 ± 17,9 U/l ($p < 0,01$).

As can be seen, the activity of LDH was honestly decreased during the vasorenal AH model. A decrease in the activity of LDH leads to the accumulation of pyruvic acid (pyruvate) in the body due to the disruption of the lactic acid formation process. The honest reduction of the CPK-MB fraction indicates the development of destructive processes and the intensification of the energy supply of the myocardium.

The effectiveness of the treatment, a fixed triple combination, was also evaluated during the study. During the determination of the fixed triple combination drug valsartan/amlodipine/hydrochlorthiazide preparation (80 / 12,5/5 mg), the level of AH in the dynamics, as well as the concentration of creatinine, residual nitrogen, urea in the blood, the activity of LDH and CPK-MB fraction were studied (Figure 1). On the 15th day of treatment, SBP decreased to an average of 100,5 ± 7,8 mmHg, and DBP decreased to 70,3 ± 1,2 mmHg. At this time, creatinine concentration was 109,1 ± 2,7 mkmol/l, residual nitrogen was 40,8 ± 2,2 mmol/l and urea was 15,4 ± 2,7 mmol/l and was statistically honest ($p < 0.05$). The activity of lysosomal enzymes increased as a result of the treatment, LDH was 291,6 ± 9,7 U/land CPK-MB fraction was - 371,9 ± 3,1 U/l [12, 13].

Although there was a change in the studied indicators in the 1st month of the treatment, statistically significant results were determined in the biochemical indicators of the blood. Against the bacpkground of the treatment, there have been cases of reduction of blood pressure to 114/50 mmHg. 1 month after treatment, creatinine concentration in blood decreased to 93,5±1,5 mkmol/l ($p < 0,01$), residual nitrogen to - 31,9 ± 0,5 mmol/l ($p < 0.01$), urea to - 11,0 ± 0,3 mmol/l ($p < 0,01$). As a result of 1 month of treatmentan increase in the activity of lysosomal enzymes has already been noted. At this time, the activity of LDH was 334,7 ± 9,7 U/l and the

CPK-MB fraction was - 460,4 ± 3,1 U/l, which was statistically significantly different from the level before treatment ($p < 0,01$).



	before treatment	15 days after treatment	1 month after treatment
CPK-MB	331.3	371.9	460.4
LDH	255	0	334.7
BUN	50.6	40.8	31.9
Creatinine	130.9	109.1	93.5

Figure 1. *The effect of valsartan/amlodipine/hydrochlorthiazide drug with fixed triple combination on blood creatinine, residual nitrogen, urea concentration, LDH and CPK-MB fraction activity.*

The increase in the activity of the LDH enzyme against the bacpkground of the treatment can be honestly explained by the regulation of carbohydrate metabolism by Angiotensin Converting Enzyme Inhibitors (ACEI). It is known that the CPK-MB fraction has the role of "carrying" macroergic phosphate compounds: it plays a special role in the process of transporting energy from the mitochondria to the cell cytoplasm [5, 6, 9]. As a result of the treatment, the CPK-MB fraction increased with statistical integrity, but the normal level of enzyme activity was not restored. The increase in the activity of the main enzyme of energy supply of metabolism shows that ACE inhibitors blocpk the renin-angiotensin system, reduce the formation of angiotensin II, and lead to the recovery of exchange processes in the body [14, 15].

Thus, in the course of the dynamic study of the lysosomal enzymes activity in the blood during the AH model, a decrease in LDH and CPK-MB fraction is observed. Their increase during the fixed triple antihypertensive treatment indicates the effect of the components of this combination on cell metabolism in different directions.

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