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RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC TOXIC HEPATITIS AND WAYS OF ITS CORRECTION

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Abstract

The aim of the study was to study the effectiveness of the long-acting angiotensin-converting enzyme (ACE) inhibitor Lisinopril in the correction of renal dysfunction in patients with chronic hepatitis (CH).It was found that in patients with CH under conditions of spontaneous diuresis, the glomerular filtration rate (GFR) decreases by 1.33 times against the background of a decrease in water reabsorption ($p<0.05$) and a tendency to a decrease in sodium excretion. During a 2-hour water load, a 3-fold decrease in GFR ($p<0.05$) was revealed with a slight decrease in water reabsorption and a decrease in sodium and potassium excretion in the urine ($p<0.05$). The occurrence of such disturbances in response to exercise indicates functional changes that may be due to intrarenal vasospasm as a result of activation of the interstitial renin-angiotensin system. The inclusion of Lisinopril at a dose of 2.5 mg in the treatment regimen had a positive effect both on the clinical symptoms of hepatitis - a decrease in the activity of ALT, AST, urea ($p<0.05$), and on the functional state of the kidneys, mainly due to

the effect on filtration processes. This is especially clearly demonstrated by the implementation of the water load: an increase in diuresis by 2 times ($p<0.05$) against the background of an increase in the glomerular filtration rate by 3 times ($p<0.05$), excretion of sodium and potassium ($p<0.05$). This indicates an increase in the adaptive function of the kidneys when included in the treatment ACE inhibitor.
Key words: chronic hepatitis; renal dysfunction; kidney; angiotensin-converting enzyme inhibitor

In a number of liver diseases, the kidneys are involved in the pathological process. Kidney damage may be preceded by a detailed clinical picture of chronic liver diseases, and in some patients it may become the leading one, which determines the need to correct these disorders [1, 2, 3]. It should be noted that hepatorenal dysfunction can manifest itself already in chronic hepatitis (CH) with minimal activity [4]. Hepatorenal syndrome (HRS) may develop in18-20% of patients with the progression of fibrotic processes in the liver and the development of liver cirrhosis (LC). HRS is based on hemodynamic disorders with minor morphological changes in the kidneys or in its complete absence [5, 6] .It is known that activation of the renin-angiotensin system (RAS) plays a significant role in the occurrence of hemodynamic disorders and development of HRS [7, 8]. RAS is the leading regulator of vascular tone, sodium and water homeostasis, the development of fibrosis in damaged tissues. It is on the effect of tissue RAS blockade that the positive nephroprotective effect of angiotensin-converting enzyme (ACE) inhibitors in various diseases is based [9]. One of the effective drugs in this group is Lisinopril which is safe in liver diseases due to the peculiarities of its pharmacokinetics. It has a nephroprotective activity that is independent of its antihypertensive effect,at least in part[10].

The aim of the study was to study the effectiveness of the long-acting ACE inhibitor Lisinopril in the correction of renal dysfunction in patients with chronic hepatitis.

Material and methods.28 patients with HCG of toxic genesis aged from 32 to 58 years with a duration of disease from 2 to 7 years were examined. The diagnosis was established according to generally accepted clinical, laboratory, biochemical, and instrumental research methods. The degree of disease activity was determined on the basis of clinical data and the activity of ALT, which did not exceed the norm by more than 3 times. BP on average was $128.10 \pm 2.11/79.75 \pm 1.48$ mmHg. The functional state of the kidneys was studied using the clearance method under conditions of 12-hour spontaneous night and induced 2-hour

diuresis.The unification of the study conditions under water load standardizes the effect on the body's water-salt homeostasis and makes it possible to accurately study the functional state of the kidneys, excluding external influences [4]. Patients with a history of organic kidney damage and marked changes in the general urinalysis were not included in the study. The control group consisted of 18 practically healthy persons of the appropriate age. The study was conducted in accordance with the Helsinki Declaration of 1975 and its revised version of 1983.

The Statistica for Windows 6.0 software package (Stat Soft Inc., USA) was used for statistical analysis of the obtained results. The critical level of significance when testing statistical hypotheses was taken as 0.05.

Research results and their discussion. Studies of the functional state of the kidneys under conditions of spontaneous 12-hour night diuresis showed minor deviations in their functioning. Against the background of almost unchanged standardized diuresis, a probable decrease in the specific gravity of urine was noted, which indicates a violation of the concentration function of the kidneys. Along with this, the concentration of creatinine in blood plasma probably increases by 40% due to a 1.33-fold decrease in the rate of glomerular filtration (GFR) (norm 132.7±13.44 ml/min).The stability of diuresis against the background of a decrease in GFR was due to a decrease in water reabsorption.

The protein concentration in the urine was close to normal, and its excretion slightly increased ($p>0.05$). Changes in the ion-regulatory function of the kidneys were manifested in a tendency to decrease the concentration of sodium in the urine with a probable decrease in the concentration of potassium and excretion by 2.2 times. Establishment of this decrease in sodium concentration in plasma by 8% ($p<0.05$) with a tendency to decrease potassium concentration can occur due to retention of ions in the intercellular space.

Carrying out the functional load revealed the following changes.In healthy individuals after two hours load the diuresis when calculated for 1 hour increased by 2 times compared to 12 hours diuresis and was on average more than 80% of the amount of water load. The total and relative diuresis was reduced by 2.5 times ($p<0.05$) and was only 1/3 of the amount of load in patients with CH in response to load. At the same time, the concentration of creatinine in the blood plasma increased by 42% ($p<0.05$) and the GFR calculated from creatinine clearance decreased almost 3 times ($p<0.05$). Thus, the degree of filtration decline exceeded the decrease in diuresis, and the latter was slightly increased compared to spontaneous only due to some decrease in water reabsorption. At the same time, more significant disturbances in the iono-regulatory function of the kidneys were also detected. The concentration of

potassium in urine and its excretion probably and sharply decreases against the background of hypokalemia ($p<0.05$). A decrease in sodium excretion ($p<0.05$) is observed due to a decrease in the mass of the functioning kidney parenchyma while the filtration charge probably decreases by 3.04 times compared to the norm (11.53±1.28 mmol/min) with very small changes in the relative sodium reabsorption.

Thus, under conditions of load quite clear, previously hidden disorders of kidney function are revealed. At the same time, the removal of water and electrolytes decreases, which, on the one hand, indicates the presence of a violation in the regulation system of ion and volume homeostasis and on the other hand, this occurs due to a decrease in GFR. The function of the tubular part of the nephron changes to a lesser extent, while the ability to reabsorb water and sodium decreases, which can have a compensatory value. The occurrence of these disorders in response to stress indicate functional changes, which may be a consequence of intrarenal spasm due to the activation of intratissue RAS.

All patients were divided into two groups during the treatment: one was prescribed standard treatment patients with CH (14 people, the control group), and the second (14 people, the main group) additionally received the drug Lisinopril in a dose of 2.5 mg once per day during 21 days. The effectiveness of the treatment was evaluated according to the following criteria: well-being and general condition of the patient, data of clinical, laboratory and instrumental examinations.Compared to standard treatment, patients in the main group noted an earlier improvement in well-being, a decrease in abdominal bloating and a feeling of fullness in the epigastric area, normalization of direct bilirubin, ALT, a decrease in AST and urea in the blood compared to the values before treatment ($p<0.05$). The inclusion of Lisinopril in complex therapy had a significant positive effect on the functional state of the kidneys in comparison with the control group during the treatment. The amount of diuresis did not differ significantly in the two groups, but the blood creatinine level decreased against the background of taking Lisinopril, although not reliably.These changes may be the result of an increase in GFR. If in the control group filtration remained unchanged, then in the main group the value of GFR tended to increase. The appointment of Lisinopril increased the release of potassium in comparison with the indicators before treatment, along with this, the concentration of potassium in the blood probably increased, reaching control values. The relative reabsorption of sodium had an increasing tendency, the filtration charge of sodium and the absolute reabsorption of sodium increased (Table 1).

Thus, the use of Lisinopril slightly increased GFR and had a positive effect on the state of the tubular processes of sodium and water transport. Taking into account that the most

significant violations of kidney function are manifested in patients with CH after load under conditions of stress, we studied kidney function during water stress against the background of taking Lisinopril. The appointment of ACE inhibitors led to an increase in diuresis in 2 hours, both standardized and relative, by more than 2 times and even exceeded the norm ($p<0.05$).This happened mainly due to a decrease in tubular reabsorption, based on a decrease in the specific gravity of urine. The level of plasma creatinine probably decreased, reaching the norm, due to an increase in GFR almost 3 times ($p<0.05$). Thus, the increase in diuresis occurred both due to an increase in GFR and due to a moderate decrease in water reabsorption. A decrease in nephron damage is indicated by a decrease in protein concentration in urine and its excretion, especially by functioning nephrons ($p<0.05$).

Table 1

Characteristics of changes in some indicators of kidney function in patients with chronic hepatitis of toxic origin in conditions of spontaneous diuresis in the dynamics of treatment (M±m)

Indexes, that were studied	Practically healthy individuals	SICK PEOPLE			
		Control group		Main group	
Diuresis, ml per 12 hours	627,92±85,41	607,59±70,30	621,78±88,51	730,05±81,09	631,02±58,90
Glomerular filtration rate, ml/min	132,71±13,44	108,75±3,2 p<0,05	112,63±8,6	98,81±4,6 p<0,05	116,08±9,42
Protein excretion, mg/100 ml of glomerular filtrate	0,370±0,159	0,576±0,211	0,432±0,094	0,586±0,122	0,316±0,174
Potassium concentration in blood plasma, mmol/l	4,42±0,36	3,69±0,21 p<0,05	3,75± 0,23	3,68±0,13 p<0,05	4,81±0,16 p_1<0,05
Sodium concentration in blood plasma, mmol/l	144,36±1,26	132,70±2,84 p<0,05	135,52±2,61 p<0,05	135,51±2,07 p<0,01	142,5±6,58

Notes: p- probability of differences compared to a group of healthy individuals; p1 - the probability of differences in indicators before and after treatment in patients of the same group.

Changes in the ion-regulatory function of the kidneys were manifested by a tendency to decrease the concentration of sodium and potassium in the urine, while sodium excretion and sodium release by functioning nephrons probably increased. The excretion of potassium probably increased, but this did not have a significant effect on the level of potassium. Changes in sodium excretion occurred mainly due to a decrease in relative reabsorption ($p<0.05$) against the background of a simultaneous increase in the filtration charge and absolute reabsorption.

Conclusions

1. The inclusion of Lisinopril in the complex therapy had a positive effect both on the clinical manifestations of the disease (improvement of the general condition, reduction of the cytolytic syndrome) and on the functional state of the kidneys mainly due to the influence on the filtration processes.

2. The positive effect of Lisinopril on kidney function in patients with chronic hepatitis of toxic genesis is manifested both under conditions of spontaneous diuresis and under conditions of water load, which indicates an increase in the adaptive function of the kidneys when included in the treatment of angiotensin-converting enzyme inhibitors.

3. The use of small doses of the angiotensin-converting enzyme inhibitors Lisinopril (2.5 mg) in the complex therapy of chronic hepatitis of toxic etiology can contribute to the prevention of the progression of renal dysfunction by reducing the activity of intrarenal RAS.

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