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НОВЫЙ ПОДХОД К КОМБИНАЦИИ ТЕРАПЕВТИЧЕСКИХ СРЕДСТВ В ЛЕЧЕНИИ БОЛЬНЫХ ВИРУСНЫМ ЦИРРОЗОМ ПЕЧЕНИ.

Резюме: В ряде исследований при применении апротинина у больных циррозом печени авторы наблюдали снижение показателей холецистокинина-8 и гастрина-17 на крысиной модели подострой интоксикации CCL4 [10.-с. 128–132.; 12.-с. 141-146]. В результате уменьшения количества короткоцепочечных пептидов в крови уменьшается влияние вегетативной нервной системы, что влияет на факторы риска, приводящие к развитию цирротической кардиомиопатии, и в конечном итоге уменьшает нарушения ритма, наблюдаемые в сердце. .

Ключевые слова: цирроз печени, CCL4, короткоцепочечные пептиды, цирротическая кардиомиопатия, ЭКГ, ЕХОКГ.

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A NEW APPROACH TO THERAPEUTIC COMBINATION IN THE TREATMENT OF PATIENTS WITH VIRAL LIVER CIRRHOSIS.

Abstract: In some studies, when aprotinin was used in patients with liver cirrhosis, the authors observed a decrease in cholecystokinin-8 and gastrin-17 indicators in the rat model of subacute CCL4 intoxication [10.-p. 128–132.; 12.-p. 141-146]. As a result of the decrease in the amount of short-chain peptides in the blood, the influence of the autonomic nervous system decreases, which affects the risk factors leading to the development of cirrhotic cardiomyopathy, and ultimately reduces the rhythm disorders observed in the heart.

Key words: Liver cirrhosis, CCL4, short chain peptides, cirrhotic cardiomyopathy, ECG, EXOKG.

Administration of the synthetic small-molecule protease inhibitor gabexate reduces elevated transaminase levels and improves the histological appearance of carbon tetrachloride-poisoned liver 24 hours after intravenous administration. In this case, TNF-α and interleukin-β1 levels were observed to decrease in rats receiving gabexate compared to rats receiving normal physiological solution. Using gabexate (aprotinin) in them, vitality was preserved even when a 20% lethal solution of carbon tetrachloride (CCl4) was injected [6. - b. 260-265].

Based on the results of the examinations, we selected 56 patients with changes in heart rhythm and prescribed them for complex treatment with a dose of 300 units of aprotinin in 100 ml of physiological solution intravenously for 3 days. The basis for prescribing this drug was the presence of changes in the ECG and EXOCG of the patients under observation. In addition, patients were recommended to drink spironolactone for a longer period than 300 mg per night.

After three months of follow-up, liver tests and short-chain peptides and some instrumental tests were repeated. Information about them is presented in tables 1 and 2 below.

Table 1

Laboratory parameters obtained before and after treatment with aprotinin and spironolactone in patients with advanced liver cirrhosis due to viral hepatitis V

Indicators	Liver cirrhosis with HBV infection n=76	
	Before treatment	After treatment
Aspartate aminotransferase unit/s*l	0,74±0,08	0,56±0,06
Alanine aminotransferase unit/s*l	0,93±0,11	0,71±0,09
Total bilirubine (mkmol/l)	47,9±5,5	29,7±4,1*
Unconjugated bilirubin (mkmol/l)	26,0±2, 7	24,0±2, 5
Cholecystokinin-8, ng/ml	2,47±0,26	1,74±0,21*
N-pro brain natriuretic peptide, pg/ml	156±2, 4	136±1, 4*

* - difference to the indicators before the treatment.

As shown in the table, no reliable changes were observed in AST and ALT values after treatments. Total bilirubin levels before and after treatment were 47.9±5.5 and 29.7±4.1 μmol/L, respectively, and the differences were reliable (R<0.001). Unconjugated bilirubin levels did not change reliably. Cholecystokinin-8 levels in the blood of patients were 2.47±0.26ng/ml before

treatment and 1.74±0.21ng/ml after treatment, which were reliably (R<0.001) decreased. N-pro brain natriuretic peptide levels before treatment and then it was equal to 156±2.4 and 136±1.4pg/ml, respectively, and reliable positive changes were observed (R<0.05).

Also, the above indicators were studied in patients with liver cirrhosis developed on the basis of chronic hepatitis C. Information about them is presented in the following 2 tables.

Table 2

Laboratory parameters obtained before and after treatment with aprotinin and spironolactone in patients with advanced liver cirrhosis due to viral hepatitis C

Markers of serum	Liver cirrhosis with HCV infection n=70	
	Before treatment	After treatment
Aspartate aminotransferase unit/s*l	0,89±0,09	0,63±0,07*
Alanine aminotransferase unit/s*l	1,26±0,13	0,89±0,09*
Total bilirubine (mkmol/l)	61,5±6,7	39,4±4,3*
Unconjugated bilirubin (mkmol/l)	34,2±4,27	26,7±3,4
Cholecystokinin-8, ng/ml	2,86±0,26	1,92±0,23*

N-pro brain natriuretic peptide, pg/ml	152±2, 4	133±1, 4*

*-reliable compared to the condition before treatment.

As shown in the table, a reliable difference was observed in AST and ALT values after treatments (R<0.001). The total bilirubin values before and after treatment were 61.5±6.7 and 39.4±4.3μmol/l, respectively, and the differences were reduced by 1.56 times and the differences were reliable (R<0.001). Unconjugated bilirubin values were 34.2±4.27 and 26.7±3.4 μmol/l, respectively, and the 1.2-fold decrease was not reliable (R>0.05).

We also compared blood peptides before and after treatments and found the following. Cholecystokinin-8 levels in patients' blood decreased 1.5 times to 2.86±0.26ng/ml before treatment and 1.92±0.23ng/ml after treatment, and the results were reliable (R<0.001). N-pro brain natriuretic peptide values before and after treatment were 152±2.4 and 133±1.4 pg/ml, respectively, and reliable positive (R<0.05) changes were observed

In our observations, a decrease in liver function tests was noted in patients with liver cirrhosis developed on the basis of HBV and HCV infections after adding aprotinin and spironolactone to its standard treatment, but these changes were reliably observed in patients with HCV infection. Because when aprotinin and spironolactone are used at the same time, they have a complementary effect and the treatment efficiency is even higher.

Hypothetically, as a result of the normalization of liver tests, the breakdown of cholecystokinin-8 improves in it, which in turn leads to stabilization of the activity of the autonomic nervous system. The listed changes, in turn, create conditions for pathological changes in the heart to shift in a positive direction. As a result, existing rhythm disorders in patients, including prolongation of the Q-T interval, are reduced.

The use of spironolactone together with aprotinin as a standard treatment for liver cirrhosis prevents and reduces fibrosis not only in the liver but also in the heart.

Treatment with aprotinin and spironolactone, based on the standard treatment of viral liver cirrhosis, led to a decrease in liver tests, short-chain peptides (cholecystokinin-8) and N-pro brain sodium uretic peptide, and improved cardiac function. Indeed, positive changes in cardiac function by overnight Holter monitoring after the treatments.

Echocardiography before and after these procedures revealed positive changes in left ventricular end-diastolic volume, left ventricular end-diastolic and systolic size and volumes, as well as a number of other parameters (Table 4).

Table 4

Pre- and post-treatment echocardiographic findings in patients receiving aprotinin and spironolactone with advanced liver cirrhosis due to viral hepatitis

Кўрсаткичлар	**Даволашдан олдин n=56**	**Даволашдан кейин n=56**	**P**
Left lobe (long axis), mm	32.16±0,13	29,9 ± 0,33	<0,001
Width of the left lobe, mm	36.16 ±0,11	34,56±1,3	>0,05
Left ventricular end-diastolic volume, ml	60.6±0,84	47,3±2,61	<0,001
The length of the right part, mm	47.16±0,1	45,46±1,4	>0,05
Interventricular wall thickness, mm	11.9±0,11	10,6±0,56	>0,05

The thickness of the back wall of the left ventricle, mm	10,6±0,1	8,9±0,1	<0,001
After the left ventricle	44,0±0,96	41,5±1,2	<0,001
Diastolic	29,6±0,095	27,7±0,7	<0,001
size, mm	87,3±1,05	74,9±2,5	<0,001
Left ventricular end-systolic size, mm	34,6±1,06	31,2±1,3	<0,001
Left ventricular end-diastolic volume, ml	135,16±2,35	130,3±3,0	>0,05
Left ventricular end systolic volume, ml	70,2±0,27	67,1 ±0,8	<0,001

When comparing left ventricular end diastolic volumes in patients with advanced liver cirrhosis due to viral hepatitis who received aprotinin and spironolactone, the values before and after treatment decreased from 60.6 ± 0.84 ml to 47.3 ± 2.61 ml, respectively, the difference between them was 21.2 % (P<0.001).

Also, left ventricular end-diastolic and systolic dimensions were 44.0±0.96 mm and 29.6±0.095 mm and 41.5±1.2 mm and 27.7±0.7, respectively, before and

after treatment. and the difference between them in both cases was equal to 6.4% (P<0.001).

In addition to the above, in our study, left ventricular end-diastolic and systolic volumes were compared before and after treatment, which were 87.3±1.05ml and 34.6±1.06ml and 74.9±2.5ml and 31.2ml, respectively. ±1.3 ml, the difference between them was 14.2% and 12.7% (P<0.001).

As mentioned above, in liver cirrhosis, the amount of cholecystokinin-8 in the blood increases in line with the decrease in liver function, and this indicates that the process of its decomposition in the liver is disturbed. As a result, it stimulates the vegetative nervous system and affects the activity of the heart, and the indicators of N-pro brain sodium uretic peptide in the blood increase, and various pathological changes are observed in the heart. Complex treatments with the addition of aprotinin and spironolactone affect this pathological ring, change the functional state of the heart in a positive direction and lead to the stabilization of the pathological process.

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