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EVALUATION OF THE EFFECT OF A NEW BLOOD SUBSTITUTE ON BIOCHEMICAL PARAMETERS IN EXPERIMENTAL TOXIC HEPATITIS

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Abstract:

Purpose of the study. Determination of the pathophysiological validity of the use of a new amino acid mixture in liver damage. Materials and methods. Acute heliotrin intoxication was reproduced by subcutaneous administration of heliotrin, 40 mg/100 g, to rats. Results. Already 72 hours after the administration of heliothrin, changes in the activity of liver enzymes were observed: the AST / ALT ratio decreased by 41%, the activity of alkaline phosphatase decreased by 21%. On the 5th day of the experiment, an increase in the activity of alkaline phosphatase by 19% was observed in the blood serum of animals. The AST/ALT coefficient in rats of the second experimental group was lower by 43%, however, the value of both coefficients did not statistically differ from those in the first experimental group. As a result of treatment, the indicators of total bilirubin and ALT significantly improved in group IV, who received the developed amino acid mixture, but there was no significantly positive dynamics in ALT and AST in group III, who received Infezol.

Keywords: heliothrin intoxication; biochemical indicators; ALT, AST, bilirubin, amino acid mixture; Infezol; experimental animals

THE AIM OF THE STUDY. Determination of the pathophysiological rationale for the use of a new amino acid mixture in liver damage.

MATERIALS AND RESEARCH METHODS. Acute heliotrin intoxication was reproduced by a single subcutaneous administration of a sublethal dose of heliotrin to rats, prepared at the rate of 40 mg per 100 g of body weight.

RESEARCH RESULTS. During the reproduction of experimental toxic hepatitis by the introduction of heliotrin, it was found that the ALT content was on average 90,5±2,51 U / L, and the AST content was at the level of 80,3±1,92 U / L. The de Rits were at 1,13±0,02. Direct bilirubin was at the level of 14,7±0,48 mmol / L, indirect bilirubin - 24,0±0,73 mmol / L. The total bilirubin was 38,8±1,08 mmol / L. Moreover, OR (odds ratio) was 0.93219976. The 95% CI (confidence interval) was 0.88765239. χ 2 = 0.9633286 (Wilconson test). Mann-Winney test (U test) was 0.87219981 at $p < 0.05$. These indicators indicate that the indicators of protein balance are in direct proportion to oxygen deficiency caused by heliotrin.

CONCLUSIONS: The developed amino acid mixture is superior to traditional methods of treatment (Infezol) in terms of the effectiveness of influence on the development and course of experimental toxic hepatitis, which is proved by the study.

RELEVANCE. One of the most common causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [5, 8-10]. The most dangerous types of hemotransmissiv infections include hepatitis B, C and D [22, 34, 39, 40]. At the same time, more than 180 hepatotoxic drugs have been identified, of which 6 groups seriously injure the liver. At the same time, 50% of drugs are hepatotoxic, especially in women this effect is more pronounced [35-38]. Medicines cause hepatocellular damage, even liver necrosis, which is clinically manifested mainly by jaundice, fever, and increased liver enzymes [21].

Autoimmune hepatitis remains hepatitis of unknown etiology, because many medical institutions do not have special examination methods, and one third of patients are referred after the development of liver cirrhosis. Autoimmune hepatitis can be suspected in any patient with acute or chronic liver disease. 80% of patients have a

recurrence of the disease after canceling the treatment [14, 41]. Timely diagnosis of chronic hepatitis and liver cirrhosis and appropriate will reduce the risk of many complications [1, 2, 4].

In patients with cirrhosis of the liver with viral etiology develop acquired thrombocytopathy, which is characterized by a decrease in the adhesive properties of platelets by 10-26% [7, 11, 13]. Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [12, 33]. Although many studies have been conducted in the last 10 years aimed at early diagnosis and treatment of complications of chronic viral hepatitis [6].

Hepatotoxicity is damage caused by exposure to a drug or non-pharmacological agent. Risk factors include: individual intolerance, age, gender, alcohol consumption, smoking, concomitant use of other drugs, liver diseases, genetic and environmental [3] At present, the creation of new, modern, effective means of metabolic correction of homeostasis in critical conditions is still continues to be relevant, the solution of which largely determines the course and outcome of the treatment of serious diseases of various etiologies. The consequences of protein deficiency, as a rule, are dysfunction of organs and systems, delayed recovery, weakening of reparative processes, a decrease in the body's resistance to infections, and anemia [23]. Recently, much attention has been paid to bioenergetic antioxidant complexes capable of restoring metabolism in cells, affecting the vital activity of the body as a whole [15, 24, 25] tissue metabolism determines the need for the use of substances that can affect metabolic homeostasis and the cellular energy-forming system [29]. Formulated mixtures of pure amino acids are the best means of influencing metabolic homeostasis, since protein synthesis occurs only from free amino acids.Nitrogen preparations used for parenteral nutrition contain all the essential amino acids in sufficient quantities, the so-called non-essential nitrogen (glycine, etc.) [16-20, 26]. Currently, there are a number of drugs widely used in medicine, balanced in terms of the content of essential and non-essential amino acids, - Infesol 40, Infesol 100 ("Berlin-Chemie", Germany), Aminoplasmal E - 5%, 10% ("B. Braun", Germany), Aminosol - 600, 800, KE ("Hemofarm", Yugoslavia). This will allow doctors to correctly apply amino acid solutions and correctly build a parenteral nutrition program. The high cost of such foreign drugs limits their widespread use in medicine [12]. In this regard, the development of domestic, more advanced metabolic means of homeostasis correction is of great importance for domestic medicine.

PURPOSE OF THE STUDY. The study of biochemical parameters in liver damage and the evaluation of the comparative effectiveness of a new amino acid mixture.

MATERIALS AND RESEARCH METHODS. To achieve this goal, a model of toxic hepatitis was reproduced using the example of heliotrin intoxication.

Acute heliothrin intoxication was reproduced by a single subcutaneous injection of a sublethal dose of heliothrin in rats, prepared at the rate of 40 mg per 100 g of body weight. Toxic hepatitis was reproduced by subcutaneous administration of heliothrin (25 mg/100 g). The material for the study is venous blood. Protein balance indicators were studied: total blood serum protein, albumin and globulin and biological materials (ALT, AST, bilirubin and alpha-amylase) by biochemical analysis using HUMAN test systems (Germany) on a semi-automatic biochemical analysis BA88A (Mindray, China). fractions will be determined by the turbidimetric method according to the generally accepted method.Animals were divided into equal groups:

Group I - before reproduction of heliotrin intoxication (intact)

Group II (control) - with heliotrin intoxication,

Group III (control, comparisons) - with heliotrin intoxication after the introduction of the reference drug "Infezol 40", within 5 days 24 hours after the last injection;

Group IV (main, experimental) - animals with heliotrin intoxication after the introduction of a new amino acid blood substitute, within 5 days, 24 hours after the last injection. Statistical processing was carried out using the Student-Fisher test.

The research results showed that the new domestic amino acid blood substitute, when studying its antihypoxic effect on the model of heliothrin intoxication, increases the resistance of experimental animals to hypoxia. In rats of the experimental group, after the introduction of the domestic amino acid blood substitute, the mice remained active during the day, no changes in behavior and functional state were observed. The condition of the coat and skin is normal without changes, they did not refuse food and water, the death of mice was not observed. On the second day and in the subsequent observation period, no pathological changes in the behavior and physiological parameters of rats were detected. The consumption of water and feed was normal, there was no lag in growth and development. There were no deaths of rats within 14 days.

In rats of the control group, after the administration of the drug, short-term lethargy and immobility were observed, which disappeared after 30-40 minutes. After 1 hour, the mice returned to their previous state, their behavior was active, and physical indicators did not deviate from the norm. On the second day and during the entire period of observation for 5 days in rats, no changes were observed in behavior and other physical indicators.During the reproduction of experimental toxic hepatitis by the administration of heliothrin, it was found that the ALT content in group 1 was on average 20.3±0.48 U/l, in group 2 the ALT content was 90.5±2.51 U/l, in group 3 group, the content of ALT was 32.7±1.06 U/l, in the 4th main group, the content of ALT was 25.9±0.53 U/l, and the content of AST in group 1 was at the level of 14.8±0.44 U/l , in group 2 the content of AST was 80.3±1.92 U/l, in group 3 the content of AST after treatment was 27.0±0.41 U/l, in the 4th main group the content of AST after treatment was 22.2±0, 36 U/l ($p<0.05$).

The number of de Rits in the 1st group was at the level of 1.38±0.03, in the 2nd group the number of de Ritz was 1.13±0.02, in the 3rd group the content of de Ritz was 1.21±0.04, in the 4th main group the number de Ritz was 1.17±0.03.

Direct bilirubin in group 1 was at the level of 3.71±0.12 mmol/l, in group 2 - 14.7±0.48 mmol/l, in group 3 after treatment - 5.31±0.24 mmol/l , in the 4th main group, the content of direct bilirubin after treatment was 3.9±0.08 mmol/l ($p<0.05$). The content of indirect bilirubin in group 1 was 9.03±0.35 mmol/l, in group 2 it was 24.0±0.73 mmol/l, in group 3 the content of indirect bilirubin after treatment was 9.79±0.25 mmol /l, in the 4th main group the content of indirect bilirubin after treatment was 8.11±0.15 mmol/l ($p<0.05$). The content of total bilirubin in group 1 was 12.7±0.41 mmol/l, in group 2 - 38.8±1.08 mmol/l, in group 3 the content of total bilirubin after treatment was 13.04±1.35 mmol /l, in the 4th main group, the content of total bilirubin after treatment was 15.1±0.46 mmol/l ($p<0.05$).Changes in some biochemical parameters of blood during heliothrin intoxication and after infusion of blood substitutes in rats (M±m)

Table 1

Animals	Intact, n=30	Control, n=22	After five days of treatment with blood substitutes:: Drug "Infezol" 40", n=28	New amino acid blood substitute, n=30
Indicators / studygroups	I group	II group	III group	IV group
ALT, U/l	20,3±0,48	90,5±2,51*** $p_1<0,0001$	32,7±1,06*, ^ $p_1<0,0001$; $p_2<0,0001$	25,9±0,53^, # $p_2<0,0001$; $p_3<0,0001$
AST, U/l	14,8±0,44	80,3±1,92*** $p_1<0,0001$	27,0±0,41*, ^ $p_1<0,0001$; $p_2<0,0001$	22,2±0,36^, # $p_2<0,0001$; $p_3<0,0001$
DeRitis	1,38±0,03	1,13±0,02* $p_1<0,0001$	1,21±0,04* $p_1<0,0001$; $p_2>0,05$	1,17±0,03 $p_2>0,05$
Bilirubin direct, μmol/l	3,71±0, 12	14,7±0,48* $p_1<0,0001$	5,31±0,24*, ^ $p_1<0,0001$; $p_2<0,0001$	3,9±0,08^, # $p_2<0,0001$; $p_3<0,0001$
Bilirubin indirect, μmol/l	9,03±0,35	24,0±0,73* $p_1<0,0001$	9,79±0,25 ^ $p_1>0,05$; $p_2<0,0001$	8,11±0,15^, # $p_2<0,0001$; $p_3<0,0001$
Bilirubin total, μmol/l	12,7±0,41	38,8±1,08* $p_1<0,0001$	15,1±0,46*, ^ $p_1<0,0001$; $p_2<0,0001$	12±0,21^, # $p_2<0,0001$; $p_3<0,0001$
Urea	4,74±0,21	5,40±0,34; $p_2>0,05$	5,1±0,22 $p_1>0,05$; $p_2>0,05$	4,9±0,17 $p_2>0,05$; $p_3>0,05$
Glucosemmol/l	4,91±0,19	5,98±0,13* $p_1<0,0001$	5,29±0,14 ^ $p_1>0,05$; $p_2<0,0001$	4,9±0,18^ $p_2<0,0001$; $p_3>0,05$
Triglycerides, mmol/l	0,89±0,02	1,18±0,04* $p_1<0,0001$	1,00±0,03*, ^ $p_1<0,0001$; $p_2<0,0001$	0,9±0,02^, # $p_2<0,0001$; $p_3<0,0001$
Cholesterol mmol/l	1,89±0,02	3,21±0,09* $p_1<0,0001$	2,16±0,05*, ^ $p_1<0,0001$; $p_2<0,0001$	1,93±0,04^, # $p_2<0,0001$; $p_3<0,0001$
albumin g/l	29,6±0,23	14,8±0,32* $p_1<0,0001$	26,4±0,48*, ^ $p_1<0,0001$; $p_2<0,0001$	28,6±0,35^, # $p_2<0,0001$; $p_3<0,0001$
globulin	39,6±0,67	28,9±1,09* $p_1<0,0001$	36,7±1,33 ^ $p_1>0,05$; $p_2<0,0001$	39,5±0,77^ $p_2<0,0001$; $p_3>0,05$
Total protein, g/l	69,2±0,64	43,7±1,07* $p_1<0,0001$	63,1±1,18*, ^ $p_1<0,0001$; $p_2<0,0001$	68,1±0,75^, # $p_2<0,0001$; $p_3<0,0001$
A/G	0,75±0,02	0,53±0,02* $p_1<0,0001$	0,75±0,03 ^ $p_1>0,05$; $p_2<0,0001$	0,73±0,02^ $p_2<0,0001$; $p_3>0,05$

Note: * - significance of differences ($p<0.05$) when comparing the results with the original data; ^ the same ($p<0.05$) when comparing the results with data obtained after heliotrin intoxication without treatment; # - the same ($p<0.05$) when comparing the results with the data obtained after the infusion of "Infezol 40".

As our studies have shown, already 72 hours after the administration of heliothrin, significant changes were observed in the activity of indicator liver enzymes: the AST / ALT ratio decreased by 41% ($p<0.001$), ALP activity decreased by 21% ($p<0.001$) compared with animals control group. The described changes in the activity of enzymes - markers of toxic liver damage indicate the active processes of damage to hepatocytes.

On the 5th day of the experiment, an increase in the activity of AP by 19% ($p<0.001$) was observed in the blood serum of animals compared to rats in the control group. There were no statistically significant differences between the activity of alkaline phosphatase in the second experimental group and the control group. The value of the coefficient AST/ALT in rats of the second experimental group was lower by 43% ($p<0.001$) compared to the

control group, however, the value of both coefficients did not statistically differ from those in the first experimental group. Lack of dynamics in the activity of AST, ALT between the first and second experimental groups indicates stabilization in the development of the pathological process due to the compensatory-adaptive mechanisms of hepatocytes.

However, the level of ALT is an unreliable marker of the pathological process in the liver.This is primarily due to the peculiarity of the laboratory method, when not the level of the enzyme itself is determined, but its catalytic activity, the rate of the catalytic reaction. Thus, the amount of enzyme is determined indirectly.

The results obtained indicate that as a result of treatment, the indicators of total bilirubin in the IV group significantly improved. The dynamics of ALT was positive in group IV, who received the developed amino acid mixture, there were no significantly positive dynamics in ALT and AST in group III, who received Infezol-40.

In general, we can say that in the case of toxic hepatitis with a 2-fold or more increase in ALT activity, intravenous therapy with Infezol with a simple cancellation of the damaging factor is not effective enough. In addition, the restoration of liver detoxification function by the end of the course of treatment, which was observed in the study group that received the developed amino acid mixture, can be interpreted as the most important indicator of the effectiveness of therapy, speaking in favor of metabolic therapy. for all values - a decrease in cytolysis and cholestasis and an increase in the detoxification function of the liver.

CONCLUSIONS.

1. As our studies have shown, already 72 hours after the administration of heliothrin, significant changes were observed in the activity of indicator liver enzymes: the AST / ALT ratio decreased by 41% ($p<0.001$), the activity of alkaline phosphatase decreased by 21% ($p<0.001$) compared to with animals of the control group. The described changes in the activity of enzymes - markers of toxic liver damage indicate the active processes of damage to hepatocytes.

2. On the 5th day of the experiment, an increase in the activity of ALP by 19% ($p<0.001$) was observed in the blood serum of animals compared to rats of the control group. There were no statistically significant differences between the activity of alkaline phosphatase in the second experimental group and the control group. The value of the coefficient AST/ALT in rats of the second experimental group was lower by 43% ($p<0.001$) compared to the control group, however, the value of both coefficients did not statistically differ from those in the first experimental group. Lack of dynamics in the activity of AST, ALT between the first and second experimental groups indicates stabilization in the development of the pathological process due to the compensatory-adaptive mechanisms of hepatocytes.

3. As a result of treatment, the indicators of total bilirubin significantly improved in group IV. The dynamics of ALT was positive in group IV, who received the developed amino acid mixture, there were no significantly positive dynamics in ALT and AST in group III, who received Infezol.

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