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PATHOPHYSIOLOGICAL RATIONALE FOR THE USE OF A NEW AMINO ACID MIXTURE FOR LIVER DAMAGE

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Abstract:

The main causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [19, 22, 23]. The most dangerous types of hemotransmissiv infections include hepatitis B, C and D [28, 30, 35, 36]. 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 [31-34].

Keywords:

The main causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [19, 22, 23]. The most dangerous types of hemotransmissiv infections include hepatitis B, C and D [28, 30, 35, 36]. 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 [31-34]. Medicines cause hepatocellular damage, even liver necrosis, which is clinically manifested mainly by jaundice, fever, and increased liver enzymes [27, 38].

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 [26, 36]. Timely diagnosis of chronic hepatitis and liver cirrhosis and appropriate will reduce the risk of many complications [16-18].

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% [21, 25, 25]. Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [24, 29]. Although many studies have been conducted in the last 10 years aimed at early diagnosis and treatment of complications of chronic viral hepatitis [20, 37, 39].

Metabolism, the formation of hypercatabolism, hypermetabolism and the development of tissue metabolic disorders determines the need to use substances capable of influencing metabolic homeostasis and the cellular energy-producing system [10]. The best means of influencing metabolic homeostasis are mixtures of pure amino acids made according to certain formulations, since protein synthesis occurs only from free amino acids. Nitrogen preparations used for parenteral nutrition contain all the essential amino acids in sufficient amounts, the so-called substitutable nitrogen (glycine, etc.) [5-8].

At present there are a number of drugs widely used in medicine, balanced by the content of essential and substitutable amino acids: Infesol 40, Infesol 100 ("Berlin-Chemie", Germany), Aminoplasmal E - 5%, 10% ("B. Brown", Germany), Aminosol - 600, 800, KE ("Chemopharm", Yugoslavia). Recently much attention has been paid to bioenergetic antioxidant complexes capable of restoring metabolism in cells, affecting the vital functions of the body as a whole [1-3]. This will allow physicians to correctly apply amino acid solutions and competently build a program of parenteral nutrition. The high cost of such foreign drugs limits their widespread use in medicine [4, 9]. In this regard, the development of domestic, more perfect metabolic homeostasis correction means is of great importance for domestic medicine.

THE AIM OF THE STUDY. To determine the pathophysiological validity of the use of a new amino acid mixture in liver damage.

MATERIALS AND METHODS OF THE STUDY. To realize the goal we reproduced a model of toxic hepatitis by the example of heliotrin intoxication.

Acute heliotrin intoxication was reproduced by single subcutaneous injection of rats with a sublethal dose of heliotrin prepared at the rate of 40 mg per 100 g of body weight. Toxic hepatitis was reproduced by subcutaneous injection of heliotrin (25 mg/100 g).

RESULTS OF THE STUDY.

It is traditionally believed that indicators such as lactate, pyruvate, glucose, derived lactate/pyruvate and glucose/lactate indices reflect the activity of anaerobic metabolism. However, along with damage to the respiratory chain, any critical condition accompanied by adrenergic stress may be the cause of a long-term increase in the values of these parameters. Therefore, the dynamics of the studied metabolic parameters is of great importance. Lactate metabolism is carried out mainly in the liver and kidneys, so along with the increased production of lactate in the tissues damaged by ischemia-reperfusion, its metabolism plays an important role, which restores the balance between lactate production and clearance.

Intoxication caused by heliotrin is a factor that actively influences the dynamics of multiple organ failure, including liver and kidney lesions due to impaired transport and extraction of oxygen by tissues, catabolism of structural proteins, stimulation

hypermetabolism in conditions of impaired nutrient delivery, glycolysis of protein molecules, development of water-electrolyte imbalance.

In the rats of the experimental group after administration of the native amino acid blood substitute during the day the mice remained active, changes in behavior and functional state were not observed. Condition of hair and skin was normal without changes, they did not refuse food and water, death of mice was not observed. On the second day and during the following period of observation, no pathological changes in the behavior and physiological indices of the mice were revealed. Water and feed intake were normal, no growth and development retardation was observed. There was no death of mice within 14 days.

Rats of the control group showed short-term lethargy and immobility after drug administration, which disappeared after 30-40 min. One hour later, the mice returned to their previous state, their behavior was active, and their physical parameters did not deviate from the norm. On the second day and during the entire observation period of 5 days, no changes were observed in the rats' behavior and other physical parameters.

Based on the data obtained, the following conclusion can be made that the new domestic amino acid blood substitute on the model of heliotrinintxication increases the survival rate of the animals, which indicates its antihypoxic effect.

The control group of rats infected with heliotrin-induced hepatitis was treated with Infesol-40 solution. Morphology of the liver.

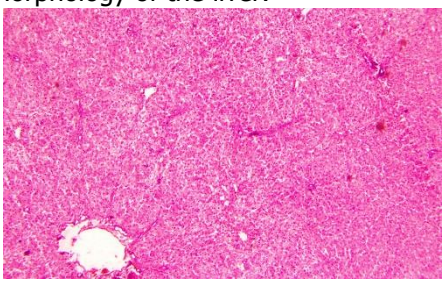

Fig. 1. Liver of rats treated with Infezol-40 solution for heliotrine hepatitis. The columnar structure of hepatocytes was restored. Cytoplasm of hepatocytes on the general background looked the same with focal staining. The coloring was almostthe same. Fatty dystrophy in the form of weakly developed drops is revealed. Sinusoidal spaces are differently enlarged. G-E staining. 4x10.

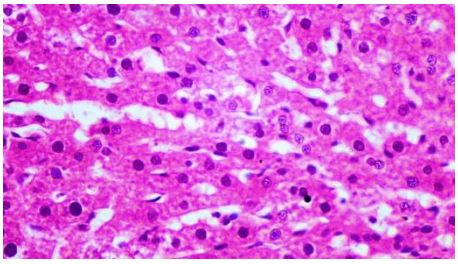

Fig. 2. Most hepatocytes look the same. Mitotic foci around hepatocytes with unicellular necrosis are revealed. The cytoplasm of hepatocytes is relatively darker. The sinusoidal spaces are enlarged cylindrically. Kupffer cells have an indeterminate outline. Disce space is mostly narrowed (4). G-E staining. 40x10.

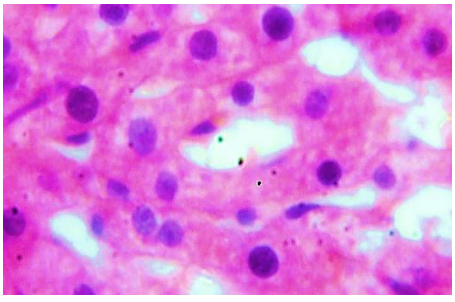

Fig. 3. In the cytoplasm of hepatocytes stained corpuscles with acidophilic foci are found. Kupffer cells are very close to hepatocytes, and Dysse cavity is almost indistinguishable. The Ito cell, which is located perisinusoidally, is activated, referring to the adjacent sinusoidal space between hepatocytes through dilated areas. Hyperchromia in the nucleus of hepatocytes. G-E stain. 100x10.

In heliotrinous hepatitis we studied the metabolites accumulating in cytoplasm of hepatocytes on the example of two abovementioned groups by the example of development of aqueous dystrophy as a result of toxic lesion of hepatocytes. Let us now consider in Fig. 1-3 microphotographs the occurrence of a number of changes in hepatocytes upon injection of Infesol-40 solution into the body of rats with this pathology.

In Fig.-1 the histioarchitectonics of the liver tissue is reconstructed in relation to the landscape in heliotrine hepatitis: columnar pairs hepatocytes, relatively uniform width of sinusoidal protrusions, relative proliferation of hyperchromic nucleated hepatocytes with 4-5 mitotic foci (Fig. 2). Chromophobia of hepatocyte cytoplasm was found to be relatively reduced (relatively acidophilic staining after infusion of Infesol-40 solution). Accuracy of hepatocyte boundaries was determined by relative narrowing of dissection cavities (dilated sinusoidal spaces in GG). The fact that most hepatocytes are relatively of the same size is proved in Figures 2, 3.

Ito cells located around the damaged hepatocytes were found to become active (Figure 3), and that they became active to close the defect around the necrotic hepatocytes around the center of the fragment. However, the relative return of endothelial cells to the sinusoidal cavity wall around hepatocytes with paranecrotic necrosis around the fragment centers and narrowing of transendothelial fissures indicate a decreased vascular response.

Morphology of the liver of rats treated with "amino acid blood substitute" solution in heliotrine hepatitis.

Recovery of the morphofunctional state of the liver of rats injected with the "amino acid blood substitute" solution was observed in heliotrine hepatitis. In particular, sodium succinate in "amino acid blood substitute" is based on stabilization of cell membrane: clear and smooth borders of hepatocyte membrane shown on Figures 4, 5, formation of more than 15-25 hyperchromatically stained nuclear hepatocytes in the 10x10 field of view. Development of sinusoidal cavities of equal width, stabilization of the lost functional state proved in Fig. 5. Fig. 6. shows homogeneous acidophilic staining of cytoplasm of hepatocytes due to regeneration and saturation of free protein structures (enzymes) in cytoplasm. In comparison with hepatocytes observed in infusion solution of Infesol-40, the effect of succinate

sodium (antioxidant) and mannitol (membrane stabilizer) in the "amino acid blood substitute" was reduction of sinusoidal cavities and interstitial tumors. Hepatocyte membrane stabilization occurs as a result of disposal of excess fluid in sinusoidal cavities and Dissé cavities.

Large-scale 14-microscopy revealed activation of Ito cells between hepatocytes.

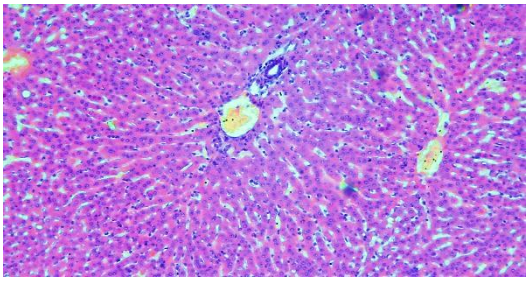

Figure 4. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. The contours of the poorly formed neutrophilic infiltration around the triads are clear. The central veins were of medium degree of fullness. The double columnar structure of hepatocytes is clear and smooth. Sinusoidal intervals were of equal width. The nuclei of most hepatocytes have a hyperchromatic appearance (contrast hue). G-E stain. 10x10.

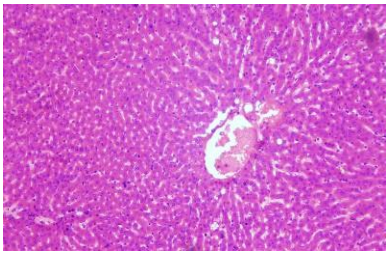

Fig.5. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. It is interesting that the liver fragment looks almost identical to the normal histioarchitectonics state. The sinusoidal intervals have the same width. G-E stain. 10x10.

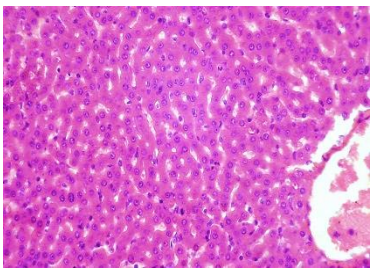

Fig.6. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. The nucleus of hepatocytes in most cases has a larger appearance and contrasting hyperchromic appearance. G-E stain. 20x10.

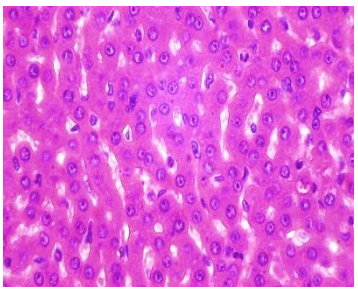

Fig.7. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. The cytoplasm of hepatocytes was stained homogeneously acidophilic. Hepatocyte membrane boundaries are clear. The nuclei are stained dark basophilic. The nuclei are also clearly visible. The sinusoidal segments are of equal width. Hypertrophy of hepatocytes around foci of unicellular necrosis. Kupffer cells are enlarged. G-E staining. 40x10.

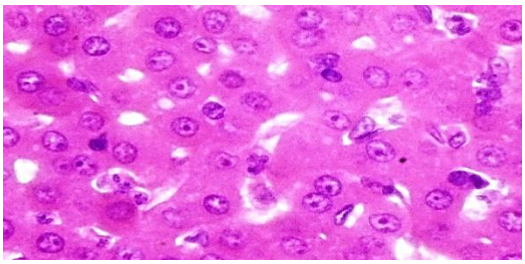

Fig.8. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. The cytoplasm of hepatocytes has acidophilic homogeneity. Foam-like structures (neutral fats) in the cytoplasm of some hepatocytes. Kupffer cells are enlarged. Disce's space is of standard width. G-E staining. 80x10.

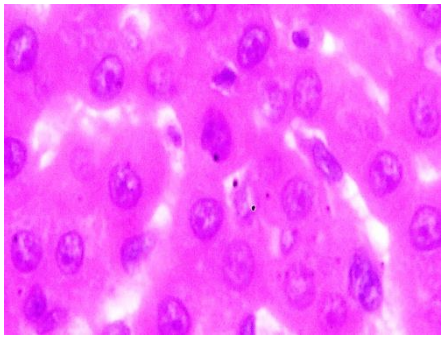

Fig.9. Rat liver with "amino acid blood substitute" solution in heliotrine hepatitis. Sinusoidal intervals are of equal width. The dissected cavity is normally visible. On the left, acidophilin is uniformly stained around chromophobic foci in the cytoplasm of hepatocytes. Hepatocyte division by mitosis around foci of monocellular necrosis. Tumor formation of Ito cells in intercellular space (activated fibrosis). G-E 100x10 staining.

Thus, Infesol-40 and the "amino acid blood substitute" solution used in heliotrine hepatitis were administered every 24 hours for 5 days. Morphological changes in the liver of rats observed regeneration of liver fragments when injected with the "amino acid blood substitute" solution. Based on the above microphotographs, almost 90-95% recovery of the liver histioarchitectonics was observed.

In contrast to the cotnrophic group the return to normal edematous dystrophy (homogeneous dark staining of cytoplasm) occurring in hepatocytes indicates the restoration of the functional state of hepatocytes. The fact that Dissé space has the same width testifies to restoration of hemodynamics in the liver and normalization of vascular response. This means that the solution of "amino acid blood substitute" has an advantage over the solution of Infesol-40 in that its components contain the necessary to ensure cellular metabolism (membrane stabilizing mannitol and sodium succinate).

The "amino acid blood substitute" solution proved to be an effective means of preventing damage to liver tissue in heliotrine hepatitis and restoring the lost morphofunctional status.

CONCLUSIONS.

1. Therapy of toxic liver injury caused by heliotrin poisoning is recommended to follow the standards of treatment of acute liver injury.

2. The use of histological methods of investigation is recommended for evaluation of the therapy efficacy. Morphological changes in the liver of rats were observed to regenerate fragments and restore histioarchitectonics of the liver up to 90-95% when injecting the solution of "amino acid blood substitute".

3. The solution of "amino acid blood substitute" was effective in preventing liver tissue damage in heliotrine hepatitis and restoring the lost morphofunctional status.

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