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TOXIC LIVER DAMAGE IN ACUTE POISONING AND ENDOGENOUS INTOXICATION

(Literature review)

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✓ ***Resume***

The authors carried out a literature review of the data on toxic liver damage in acute poisoning, due to the interaction of biochemical structures ("toxicity receptors") of the human body with toxic substances of various origins. Drug poisoning by a number of researchers in different countries (USA, Uzbekistan) leading to deaths, the authors review the data, find out the reason for how the liver changes, which subsequently leads to endogenous intoxication

Key words: liver, drugs, poisoning, intoxicatio

ТОКСИЧЕСКИЕ ПОРАЖЕНИЯ ПЕЧЕНИ ПРИ ОСТРЫХ ОТРАВЛЕНИЯХ И ЭНДОГЕННОЙ ИНТОКСИКАЦИИ

(обзор литературы)

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✓ ***Резюме***

Авторами проведено литературный обзор данных токсические поражения печени при острых отравлениях, вследствие взаимодействия биохимических структур («рецепторов токсичности») организма человека с токсическими веществами различного происхождения. Отравления лекарственными средствами ряда исследователей в разных странах (США, Узбекистан) приводящие в летальные исходы, авторами проводится обзор данных, выясняется причина, как изменяется печень, которая в последующем приводит к эндогенной интоксикации

Ключевые слова: печень, лекарственные средства, отравление, интоксикация

O'TKIR ZAHARLANISH VA ENDOGEN INTOKSIKATSIYA PAYTIDA JIGARNING TOKSIK SHIKASTLANISHI

(Adabiyot sharhi)

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✓ ***Resume***

Mualliflar inson tanasining biokimyoviy tuzilmalari ("toksiklik retseptorlari") ning turli xil kelib chiqadigan toksik moddalar bilan o'zaro ta'siri tufayli jigarni zaharlanishida toksik shikastlanishlari to'g'risidagi ma'lumotlarning adabiy sharhini o'tkazdilar. Turli mamlakatlarda (AQSh, O'zbekiston) o'limga olib keladigan bir qator tadqiqotchilar tomonidan giyohvand moddalardan zaharlanish, mualliflar ma'lumotlarni ko'rib chiqadilar, jigarning qanday o'zgarishini, keyinchalik endogen intoksikatsiyaga olib kelishini aniqlaydilar.

Kalit so'zlar: jigar, dorilar, zaharlanish, intoksikatsiya

Relevance

In the modern view, acute poisoning is a pathological condition resulting from a violation of chemical equilibrium, due to the interaction of biochemical structures ("toxicity receptors") of the human body with toxic substances of various origins [3, 13, 31]. Toxic hepatitis is one of the most common types of pathology caused by the action of various chemicals, including drugs, pesticides, alcohol, etc., as well as various endotoxins, including protein breakdown components in burn toxemia, peritonitis, and pancreatic necrosis [1, 32]. Medicines are usually represented by substances with powerful biological activity and therapeutic efficacy, but most of them have a potential hazard and often have serious consequences leading to disability or death [4, 12].

According to a number of researchers, only 13-15% of new drugs entering the market meet modern requirements of pharmacodynamics and pharmacokinetics, safety, while often the toxic property of a drug is detected only after it enters the pharmacy network.

In the USA, according to the US Food and Drug Administration products and drugs (FDA), complications caused by the use of drugs account for up to 25% of all causes leading to an increase in the mortality rate of the population, being in fourth place after cardiovascular, oncological and acute cerebrovascular accidents [8, 12]. According to the latest statistics, in the United States, the negative impact of drugs, annually leads to the death of about 120-125 thousand people [8].

We are well aware of and often used in the process of self-treatment of fever and pain syndrome, the so-called "harmless" drug paracetamol, but it is he who is the leader in the United States and the European Union in the number of cases of overdose and poisoning, leading to severe liver damage and even death .

As for Uzbekistan, due to the lack of reliable statistical information related to the identification of side effects of drugs and their overdose, we can only assume that the real situation with drug intoxication of the population is no less complicated than in developed countries [8].

In recent years, the hepatotoxicity of the sharply increased amount of drugs used in medical practice has become one of the main problems of clinical toxicology [4, 8].

Currently, experts in pharmacological safety have identified about 1200 drugs with toxic effects on the liver and leading to the process of their application to damage to parenchymal cells with the development of drug-induced hepatitis of varying severity [11, 17].

Toxic hepatitis caused by the use of drugs in medical activities causes 5 to 12% of all hospitalizations for hyperbilirubinemia, that is, jaundice and up to 15-17% of cases of acute liver failure. In this regard, the artificial formation of drug-induced hepatitis has become a mandatory part of all preclinical trials of hepatoprotectors [11, 12].

Most of the drugs taken orally into the body are lipophilic, non-polar substances, and therefore the transfer of their molecules through the bilipid layer of the cell membrane of the intestinal epithelium occurs by passive transport along the concentration gradient, or if they are hydrophilic polar substances, then their absorption occurs with the help of such transport proteins as albumin [8, 11, 12].

In the liver, further elimination of medicinal substances is carried out by their transformation from non-polar hydrophobic compounds into polar hydrophilic ones, as well as other stages of biotransformation of foreign compounds. This process occurs with the participation of enzymes of hepatocytes (monooxygenase), which are located in microsomes and the Golgi complex, while the main active component of oxidation processes are the multienzyme complex hemoprotein cytochrome P450 and the coenzyme nicotinamide-adenine-dinucleotide-phosphate (NADPH) [8, 9 , 21, 32].

Clinical toxicologists and other researchers of the toxicity of medications have found that if you take paracetamol in a dose of no more than 4 grams, then complications in the form of toxic liver damage are unlikely. However, long-term, that is, more than three days, the use of paracetamol in doses exceeding 5 grams per day, as well as a single dose of more than 15 grams of the drug, cause a high risk of developing liver dysfunction due to its organic damage. The main danger is the formation of toxic metabolites such as N-acetyl-benzoquinone-imine (NAPQI) as a result of oxidation on cytochrome P450 by the mechanism of lethal synthesis [23, 25, 28, 30].

At the same time, an overdose of paracetamol leads to a decrease in the reserves of glutathione, which is the main blocker of its destructive effect on the liver, as a result, toxic metabolites bind to the proteins of the cell membranes of hepatocytes, which leads to massive necrosis of the hepatic parenchyma. At the same time, researchers especially noted a sharp increase in the hepatotoxic effect of paracetamol when combined with ethyl alcohol [3, 19, 20, 21, 23].

The main reason for the development of toxic hepatitis remains the abuse of alcohol and its

surrogates. Toxic alcoholic hepatitis, which is based on dystrophic and necrotic changes in the liver parenchyma, is accompanied by a violation of all its vital functions. Liver damage is manifested by a decrease in synthetic, detoxification and regulatory (influence on interstitial and other types of metabolism) functions [1, 4, 13, 18, 27]. Most often, acute alcoholic hepatopathy occurs in the form of cytolytic syndrome, which is understood as a violation of the permeability of the cellular and intracellular membranes of hepatocytes. The clinical manifestations of this syndrome are a sudden increase and soreness of the liver, icterus of the sclera and skin, phenomena of general intoxication, fever, and in advanced cases - hepatic encephalopathy. The products of destruction of the liver parenchyma are directly involved in the formation of endogenous intoxication, which, in turn, leads to an increase in degenerative-dystrophic changes in the liver and other parenchymal organs, contributing to the development of complications, including infectious [9].

Also, the liver is one of the main target organs in the name of endogenous intoxication (EI), which develops in various diseases as a result of the accumulation of various toxicants of endogenous origin in the body with insufficient function of the natural biological detoxification system [9].

The first data on the development of endotoxicosis in acute poisoning with cauterizing agents, neurotropic poisons (barbiturates, alcohol, carbon monoxide, organophosphorus compounds) were published by E.A. Luzhnikov. et al. in 1989. The authors proved that already from the toxicogenic stage of acute poisoning, there is an increased level of CM in the blood and an increase in hematological indices of intoxication (leukocyte index of intoxication, neutrophil shift index), as well as a decrease in the binding capacity of albumin, the shifts of which deviated from the norm by 1.4-3, 4 times [13, 14, 15].

Despite the significant molecular, biochemical and clinical difference in endotoxicosis, one of the main target organs for toxins is the liver with the formation of toxic hepatitis (TG), the severity of which directly depends on the concentration and duration of exposure to EI factors [7].

A separate group of victims with changes in liver function is represented by patients with extensive and deep burns. The phenomena of hepatitis are observed in all periods of burn disease [9, 24, 29]. Violation of vascular permeability, which is noted immediately after a burn injury, reaches its peak after 6-8 hours, when a decrease in the volume of circulating blood becomes obvious. As a result, there is a transition of intravascular fluid into the interstitial space of intact tissues. In the burned tissues, the osmotic pressure rises, which serves to increase the flow of fluid into this zone and to increase the edema, which is caused by an increase in sodium ions in them. The osmolarity of the intestinal fluid increases even more due to the subsequent release of proteins from the vascular bed into it, mainly albumins, which have the ability to retain water 17 times greater than the mass of the protein itself. The development of edema in unburned tissues, which is especially pronounced in burns of over 30% of the body surface, largely depends on the loss of protein circulating in the vascular bed. In severe burns, due to a violation of the permeability of cell membranes, sodium ions from the extracellular space penetrate into the cells and carry water with them, which threatens the development of intracellular edema [3, 19, 32].

The developing hypovolemia becomes the cause of hemodynamic disorders, expressed in a drop in cardiac output, an increase in total peripheral vascular resistance, a decrease in central venous pressure, pulmonary artery pressure and general systemic pressure, causing a further decrease in regional blood flow in the kidneys, liver and pancreas. At the same time, increasing hemoconcentration with hypercoagulation, impaired blood rheology (deterioration of erythrocyte deformability, increased viscosity) lead to further microcirculatory tissue changes, which are manifested by secondary necrosis in the heat-affected zone, the appearance of acute erosions and ulcers in the gastrointestinal tract, early pneumonia, the development of hepatic renal and cardiopulmonary failure [32].

According to the toxicological and combustiological centers of the CIS, the European Union, and the United States, liver damage occurs in 25-47% of patients admitted with acute chemical poisoning, from 60 to 95% of all cases of toxic hepatitis occurs as a result of severe endogenous intoxication [9, 22, 32].

Hepatotropic poisons, their metabolites and endogenous toxins cause various chemical reactions in the cell - depletion of reduced glutathione or oxidative stress, followed by an effect on proteins, lipids and DNA. This leads to apoptotic cell death and an increase in the effect of cytokines on the liver immune system, since the process involves cell organelles - mitochondria, cytoskeleton, endoplasmic reticulum, microtubules and nucleus [25]. According to a number of authors, an indirect effect of xenobiotics on cell organelles is possible through the activation or inhibition of signal kinases, transcription factors, and the expression of profile genes. The outcome

may be the start of a necrotic or apoptotic process, or an increase in the effect of cytokines on the immune system [3].

The liver is a barrier to virtually all foreign substances entering the human body. Entering the body in various ways, hepatotoxic agents disrupt the structure and function of the cell membranes of hepatocytes, enhance the processes of lipid peroxidation, change the processes of regeneration and function of hepatocytes, which is accompanied, directly and indirectly, by impaired immune reactivity [3].

Toxic liver damage can manifest itself in acute and chronic forms. Acute liver damage is characterized by necrosis and fatty degeneration of liver cells, hemodynamic disorders, edema and protein degeneration of cells. It develops 2-3 days after exposure to a damaging agent and is accompanied by an increase in body temperature, weakness, loss of appetite, pain in the right hypochondrium, intense coloration of urine, yellowness of the sclera and skin [3, 32]. Development of hemorrhagic and hepatorenal syndromes is possible. In contrast to acute toxic hepatitis, the clinical picture of chronic toxic liver lesions is not expressed, characterized by a relatively benign course without a tendency to progression. There are practically no clear signs of liver failure and outcomes in liver cirrhosis. Chronic toxic hepatitis (CTG) in terms of clinical and morphological signs and course is closest to the so-called nonspecific reactive hepatitis. Despite the duration of the process, no lethal outcomes occurring directly as a result of liver damage are observed. HTG has a long course with periodic exacerbations, usually due to overwork or an error in the diet. For CTG of professional genesis, a gradual development of the disease is characteristic, starting with dyspeptic complaints, the addition of biliary syndrome, moderate enlargement of the liver and impairment of its functional state. Examination of the patient for markers of viral hepatitis B, C and D allows to exclude the viral etiology of the disease. Ultrasound examination of the liver and biliary tract is of great diagnostic value. In difficult cases of diagnosis, it is recommended to use computed tomography (CT) to determine the density of the liver [3, 32]. CT scans the liver in sequential horizontal sections. Diagnostics of TG includes the establishment of hepatitis based on the level of bilirubin and its fractions, albumin in the blood and prothrombin index (decrease), activity of transaminases, alkaline phosphatase and gammaglutamyl transpeptidase and exclusion of viral etiology of the disease. It is necessary to take into account other symptoms of intoxication, changes in the blood, nervous system [3, 32].

Genetic studies [7, 12], which were widely carried out in persons who were in contact with radiation, beryllium, microwave ovens and suffered from occupational allergic dermatoses, are an urgent direction in the study of toxic hepatitis. The data of such studies, in combination with clinical and functional characteristics, help to identify a predisposition to the disease and identify individuals with an individual predisposition to certain occupational hazards.

As you know, the processes of biotransformation of xenobiotics proceed with the participation of cytochrome P450 in the liver, are associated with the formation of aggressive intermediate products and the initiation of free radical processes, while liver damage and the development of toxic hepatitis develop. One of the members of the cytochrome P450 family is CYP2E1. The CYP2E1 gene is mapped on chromosome 10 in the 10q24.3 region and is expressed mainly in the liver [27, 30, 32].

Thus, genetic research is a topical direction in the study of toxic hepatitis. In Uzbekistan, the study of predisposition to chronic (industrial) toxic hepatitis was widely carried out in 2006-2009. According to T.O. Daminov. the features of the distribution of HLA-antigens in patients with chronic viral hepatitis in the Uzbek population, and in patients with CTG of professional genesis were studied. HLA-typing was carried out in the tissue typing laboratory of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan using a standard two-stage microlymphocytotoxic test. The results of the study showed that antigens were most often detected in patients with CTG: A2, A25, B16, B8, B22. All these antigens were statistically significant. The presence of these antigens in the HLA phenotype of individuals increases the risk of developing TG in their owners. HLA haplotypes have also been studied. Significance was established for haplotypes A2 / B8, A2 / B15, A 25 / B22, the inheritance of which increases the risk of developing TG. The data obtained indicate the presence of HLA-associated genetic control in the transmission of susceptibility to CTG in the Uzbek population [3].

These studies suggest their effectiveness in the study of hereditary predisposition to acute toxic hepatitis due to exposure to exotoxins and toxic liver damage during endogenous intoxication, but such studies have not yet been carried out [30].

In recent years, a lot of works on toxic liver damage have been published, however, there is still no unified view of the pathogenesis of the

development of toxic hepatitis, there are no clear diagnostic criteria to differentiate it from infectious at an early stage, the role of hypoxia and oxidative stress in the development of liver damage in severe poisoning, morphological differences in changes in the structure of the liver in acute chemical poisoning of various etiologies and in endogenous intoxication have not been studied [18, 32].

Also, the relationship between toxic liver damage in acute chemical poisoning and the immune status of the body has been insufficiently studied. The absence of clear diagnostic criteria for TG in acute chemical poisoning at an early stage leads to its late diagnosis, in fact, already at the stage of development of liver failure and, accordingly, late and inadequate drug correction. Accordingly, we believe that the inclusion of antioxidant, antihypoxant, membrane-protective and immunomodulatory properties into the complex of therapeutic measures will be of great importance in the prevention and intensive therapy of toxic liver damage [16, 32]. The use of hepatoprotectors can reduce the damaging effect of lipid peroxidation products and improve the reparative processes in the liver, and the use of immunomodulators affects the immune system, correcting developing disorders, and improving the reparative processes in hepatocytes [16].

However, an algorithm for their use in toxic hepatitis at an early stage of acute poisoning has not yet been developed.

Analysis of the literature and the work of the toxicological and burn departments of the Republic of Uzbekistan showed the absence of a single, differentiated by the severity of poisoning approach to the tactics of TG intensive therapy. In addition, in our country, at the level of sub-branches of the RSCEMP, patients with acute poisoning are admitted not to specialized toxicological, but to intensive care units. This situation leads to the dependence of the quality of care provided on the qualifications and experience of the doctor. In this regard, there is an urgent need to create a unified algorithm for therapeutic measures based on a clear and generally accepted methodology for assessing the severity of the condition in toxic hepatitis.

Extensive thermal trauma is accompanied by the development of a nonspecific systemic inflammatory response syndrome - CVS, which underlies the complications of burn disease and high mortality. The developing uncontrolled CVS becomes the cause of tissue damage, immunodeficiency with the development of purulent-septic complications, followed by multiple organ failure. Studies show that toxic hepatitis in severely burned patients who are hospitalized in the RSCEMP develops in 82.9% of cases [9].

Thus, the above unresolved issues in the diagnosis and tactics of intensive therapy of toxic hepatitis in exo- and endotoxicosis require further research.

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