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MODERN VIEW ON A PROBLEM OF TOXIC LIVER DAMAGE

Toxic liver damage is caused by various toxic agents: household chemicals, pesticides, alcohol, harmful substances of industrial origin and drugs [1].

Among the U.S. population in 2003, 44% of all deaths from liver disease were related to alcohol abuse [2].

A large proportion of all toxic hepatitis is due to medication. Liver plays a leading role in the metabolism and biotransformation of most drugs. In Western countries, drug-induced liver injury (DILI) is reported to be a major cause of acute liver failure [3]. It is known that DILI remains one of the main reasons for drugs withdrawal from the market [4].

Alcohol. The WHO estimates that alcohol is now the third highest risk factor for premature mortality, disability and loss of health worldwide [5].

To date, the pathogenesis of alcoholic hepatitis remains incompletely clear. Various factors play a role in its development, including genetic, nutritional, metabolic, immunological, environmental factors, and others. However, the two main pathogenetic mechanisms – oxidative stress and cytokine / endotoxin-mediated damage – are leading in the development of acute alcoholic hepatitis [6].

Tetrachloromethane. It has been established that the pathogenetic effect of CCl_4 is due to free-radical products formed in the course of its metabolism with the participation of the cytochrome P-450-dependent monooxygenase system. The formed chemically active radicals $CCl\cdot$ and, in the presence of oxygen, $CCl_3OO\cdot$ are inducers of lipid peroxidation of cell membranes. They interact with unsaturated fatty acids, as a result of which lipid peroxyl radicals are formed, which trigger a cascade of chain reactions with the formation of products with radical properties. Thus, the prooxidant effect of CCL_4 is realized [7; 8].

The incidence of DILI ranges from 1 per 10,000 to 1 per 100,000 population [9,10]. An Icelandic study reported a frequency of 19 per 100,000 population, with a much higher risk for some drugs (eg, for azathioprine, this ratio is 1 in 133) [11]. According to sources [12], toxic liver damage caused by the use of drugs accounts for up to 10% of all adverse reactions.

Drugs can have direct and indirect (toxicity of its metabolites) hepatotoxicity (HT), as well as cause the development of individual intolerance reactions. It is reported that approximately 75% of idiosyncratic reactions to drugs lead to the need for liver transplantation or death [13]. DILI is most often caused by cytostatics, anti-TB drugs, drugs used in chemotherapy treatment regimens in oncology, antibiotics, nonsteroidal anti-inflammatory drugs, cardiovascular, neuro- and PT drugs, i.e. virtually all modern drugs [12]. In addition, it is reported that more than 1,000 herbal drugs can cause the development of DILI [14].

Anti-TB drugs. Anti-TB drugs are one of the commonest groups underlying idiosyncratic HT worldwide. Overall, HT attributed to anti-TB drugs has been reported in 5%–28% of people treated with anti-TB drugs. Formation of reactive metabolites has been implicated in a range of clinical toxicities including a proportion of those classified as 'idiosyncratic' DILI. Reactive metabolites are generally electrophiles. When they escape detoxification, they react with nucleophilic groups such as lysine and cysteine on cellular proteins. Covalently modified cellular proteins can either be repaired or degraded. If these processes fail, drug-metabolite adduct formation itself impairs important cellular function leading to the manifestation of target organ injury. Generation of reactive metabolites followed by covalent protein binding can also lead to immune mediated injury [15; 16].

Psychotropic (PT) drugs. All families of PT agents can cause liver injury. The most common event is acute injury with various patterns, including hepatocellular, cholestatic, or mixed injury. PT agents are among the main causes of cholangitis and ductopenia, which mimic chronic biliary disease but with a better prognosis; compounds that are particularly involved include tricyclic antidepressants and phenothiazines [17]. HT of PT drugs can be realized by the following mechanisms: cytochrome P450 activation and therefore inhibition of metabolism of substances competing for the same metabolic pathway; inhibition of transmembrane transport and the work of Na-K-ATPase in hepatocytes; electrostatic precipitation of bile acids in liver cells and bile ducts. In addition, there is evidence in favor of the immunoallergic

mechanism of damage [18]. However, despite intensive investigation, HT mechanisms remain unknown for the majority of PT agents [19].

In most (80-90%) cases, DILI has a favorable prognosis with complete recovery. About 10% of cases can turn into a chronic form, the criterion for the establishment of which is an elevated level of liver enzymes in the blood for more than 6-12 months. Approximately the same proportion of patients die [13].

Conclusions. Liver, being the central organ of metabolism, is prone to toxic damage. Different compounds can have direct or indirect HT, or cause idiosyncratic reactions with three-quarters of idiosyncratic reactions necessitating liver transplantation or leading to death. Nevertheless, many mechanisms of DILI remain unknown, which forms a basis for future research.

Drug-induced hepatitis takes an important place among all toxic hepatitis and is one of the main causes of liver failure. Toxic hepatitis accounts for up to 10% of all adverse drug reactions.

Despite the fact that a large percentage of patients with DILI is fully recovered, about 10% of cases become chronic; about the same proportion of patients die.

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