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The current state of the problem of drug hepatotoxicity and measures of its prevention and treatment

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Summary:

Drug use is one of the most important causes of liver damage and ranks 3rd after viral diseases and alcohol.

Hepatotoxicity of drugs remains one of the urgent problems of modern medicine, as it leads to a decrease in the effectiveness of pharmacotherapy, development of serious complications that can cause disability and death. Such a side effect increases the length of stay of patients in the hospital and increases the cost of treatment. That is, the problem of hepatotoxicity is not only a medical, but also a social problem.

Research sources focused on modern views about drug hepatotoxicity are reviewed and summarized and new approaches to its prevention and treatment are analyzed.

Conclusions. Hepatotoxicity of drugs remains one of the urgent problems of modern medicine, as it leads to a decrease in the effectiveness of pharmacotherapy, development of serious complications that can cause disability and death. Such a side effect increases the length of stay of patients in the hospital and increases the cost of treatment. That is, the problem of hepatotoxicity is not only a medical, but also a social problem.

Key words: drug hepatotoxicity, measures of its prevention and treatment, new approaches.

Each year, the incidence of hepatotoxicity ranges from 1.27 to 40.6 cases per 100,000 patients. However, their number has increased 30 times over the past 10-15 years, mainly due to the introduction of new drugs into clinical practice and the increase in the aggressiveness of such treatments. In the structure of liver diseases, the frequency of drug-induced liver damage (Drug-Induced Liver Injury (DILI)) averages 5-7% and is the main cause of acute hepatitis in 30% of patients over 40 years of age and of fulminant liver failure requiring liver transplantation in 25% of cases, and in 10% it can lead to the death of the patient [1, 2, 3].

DILIs in Ukraine make up 50% of the total structure of acute jaundice and they are the main cause of acute liver failure, and it is precisely because of them that drugs are most often recalled and withdrawn from circulation. In the general structure of side effects due to taking drugs, hepatotoxicity is 10%. In the USA, approximately 2,000 cases of acute liver failure are registered annually, of which more than 50% are due to drugs (39% — acetaminophen, 13% — idiosyncrasy reactions as a result of the action of other drugs) [4].

Among hospitalized patients, the frequency of DILI is 0.7%-1.4%, but among patients with jaundice, it’s about 5%, and the cause of its occurrence were precisely drugs [1, 2]. Therefore, DILI today still remains a difficult clinical problem, as the spectrum of their clinical and morphological manifestations is extremely broad the diagnosis is established by exclusion and there are no clear principles of therapy, except for the withdrawal of the "causal" drug.

Factors contributing to the development of DILI depend both on the pharmacological properties of the drug (chemical structure, lipophilicity, dose, duration of use, as well as the simultaneous use of several drugs (polypharmacy)), as well as on the individual characteristics of the patient's body. In particular, on age and sex, ethnicity, alcohol consumption, presence of co- and polymorbidity, chronic liver diseases, as well as genetic characteristics of the patient's body. Under certain conditions any drug can cause liver damage.

Today, it is known that about 1,200 drugs of almost all pharmacological classes can cause DILI and about 200 more are potentially hepatotoxic drugs. However, the frequency of liver damage for each drug varies from 1:1,000 to 1:100,000 [1,2,4] .

According to pharmacoepidemiological studies, DILI most often develops against the background of taking NSAIDs, antituberculosis, antibacterial drugs, analgesics, hormonal, cytostatic, hypotensive, antiarrhythmic drugs and drugs that affect the central nervous system, which is a consequence of not only their potential hepatotoxicity, but also of the frequency of

use. In etiological terms, the first place is occupied by antituberculosis and antibacterial drugs, then NSAIDs, drugs that regulate the functions of the nervous system, hormonal, cytostatic, hypotensive, antiarrhythmic drugs. The results of research into the etiology of acute liver failure have shown that drugs are its main causes in the USA, European countries, and Japan. In the USA and Europe, idiosyncratic drug-induced reactions are the most common cause of DILI, while the use of traditional complementary and dietary supplements is the main cause of DILI in Asian countries [5].

According to the mechanism of pharmacological action, DILIs are classified into two groups:

1) induced by direct toxic effects of drug on the liver tissue;
2) idiosyncratic.

Direct toxicity of drugs is seen in a significant share of patients exposed to the drug, it is predictable, develops within a short time (from hours to days from the moment of taking the drug) and is dose dependent. Idiosyncratic drug-induced hepatitis, as a rule, is not related to the dose of the drug, belongs to unpredictable reactions caused by the individual characteristics of the patient's body. Liver damage can be latent or manifest after a long time after taking the first dose and progress regardless of withdrawal of the drug. It is idiosyncratic reactions that make up the majority of cases of DILIs, which determines their clinical significance.

Drugs that have a direct hepatotoxic effect include acetaminophen, amiodarone, anabolic steroids, antiretroviral drugs, valproic acid, heparins, and statins.

At the same time, any drug can potentially cause an idiosyncratic reaction, as it depends on the genetic characteristics of the patient and the immune reactivity of the body. Most often, amiodarone, amoxicillin / clavulanic acid, allopurinol, diclofenac, isoniazid, ketoconazole, lisinopril, statins, sulfonamides, fenofibrate, contraceptives, levofloxacin, phenobarbital [6] can cause hepatotoxicity.

Clinical and morphological manifestations of DILI vary from asymptomatic elevation of liver enzymes to fulminant failure and decompensated liver cirrhosis. Acute DILIs are usually divided into three main forms: hepatocellular, cholestatic and mixed. For the hepatocellular type a characteristic increase in the level of alanine aminotransferase (ALT) more than 2 times the upper limit of normal (ULN), a normal level of alkaline phosphatase (AP) and the R ratio (the ratio of ALT and AP levels) ≥5 are usually present. If the level of ALT is within normal values, and the level of AP reaches more than 2 times ULN with the R index ≤2, the

cholestatic type is diagnosed. Mixed type is characterized by an increase in ALT and AP levels more than 2 times ULN and with an R index = 2-5.

According to the degree of severity, DILIs are classified into mild, moderate, severe and fatal, or those requiring liver transplantation. Mild DILI is characterized by an asymptomatic increase in the level of ALT or AP, as well as a moderate increase in the level of total bilirubin (no more than 2 times ULN). A moderate degree of severity of DILI is accompanied by an increase in the activity of ALT or AP, total bilirubin over 2 ULN against the background of such clinical symptoms as weakness, nausea, vomiting, pain in the right upper quadrant of the abdomen, itching, skin rash, jaundice, lack of appetite, weight loss. Severe degree DILI is characterized in addition to increased cytolysis and cholestasis also by the onset of coagulopathy (international normalized ratio ≥1.5) or the presence of ascites, hepatic encephalopathy and failure of other organs. The highest degree of severity of DILI is death or the need for liver transplantation to prevent it [1].

Diagnosis of DILI includes:

- careful collection of anamnesis: find out the list and quantity of drugs taken by the patient (medications, nutritional supplements, medicinal herbs), the duration of their use and doses, the possibility of their use by the patient in the past, evaluate the interval between the start of the use of drug and the development of liver damage;
- assessment of the dynamics of clinical symptoms and detected laboratory syndromes characterizing liver damage in response to suspected drug withdrawal;
- taking into account specific risk factors of DILI (alcohol consumption, pregnancy, chronic and acute diseases, hereditary and allergic history);
- exclusion of other possible causes of liver damage (viral hepatitis, autoimmune hepatitis, mechanical jaundice, primary sclerosing cholangitis);
- taking into account previously known data on the hepatotoxicity of the drug;
- careful assessment of the patient's condition after repeated (accidental) administration of the drug;
- morphological study of a liver biopsy [2].

According to the Swedish Register of Adverse Drug Reactions, the highest mortality (12.7%) is characteristic of the hepatocellular form of DILI, followed by the cholestatic form (7.8%) and mixed (2.4%). It should be noted that the same drug can cause different forms of DILI. A prospective analysis of 69 cases of hepatotoxicity caused by amoxicillin / clavulanate showed that the form of DILI may depend on the duration of use: in the first week of

treatment, the hepatocellular type of damage prevails, in the second-third - cholestatic and with longer therapy - mixed [11].

It is known that some antibacterial drugs can cause dose-dependent toxic damage of the liver, which can occur both against the background of taking a high single dose or a high cumulative dose that accumulates in the body during long-term use of the drug. Dose-dependent DILIs are most often observed with intravenous administration of high doses of tetracyclines, especially during pregnancy or in the postpartum period [10]. Nevertheless, the majority of DILIs that develop with the use of antibacterial agents are idiosyncratic in nature [6].

It is believed that the basis of the idiosyncratic reaction is a genetic predisposition associated with the polymorphism of multiple genes that regulate the activity of enzymes, participate in the metabolism and transport of drugs, the presence of certain antigens of the HLA class, hyperproduction of cytokines and mitochondrial DNA mutations. In particular, this assumption is supported by a strong correlation between the presence of the HLA-B * 5701 allele and flucloxacillin-induced liver damage [9]. However, a combination of several risk factors, including non-genetic ones, is probably necessary for the development of DILI. The latter include gender, age, nutritional status of the patient, alcohol consumption, presence of initial liver damage and concomitant diseases (for example, diabetes and HIV infection), degree and pathway of drug metabolism, drug interactions [2,4].

Idiosyncratic reactions, in contrast to reactions caused by the actual toxic effect of the drug, are considered dose independent. However, this is true only in certain cases. The relationship between the daily dose of a drug and the frequency of development of DILIs was found in at least two studies. In particular, it was shown that drugs prescribed in doses of less than 10 mg / day rarely cause DILI, and the results of the analysis of 598 cases of DILI suggest that the frequency of development of this complication, as well as of its adverse results, is significantly reduced if the daily drug dose does not exceed 50 mg. Moreover, 81% of all cases of acute drug-induced liver failure (excluding cases associated with the use of paracetamol) in the United States, which required liver transplantation, were caused by drugs used in a dose of more than 50 mg / day [5,8].

One of the main mechanisms of the development of DILI is considered to be the formation of reactive drug metabolites capable of binding to endogenous macromolecules and exerting a direct toxic or indirect immunological effect on the liver. This is confirmed by the results of a recent study conducted in the USA, analyzing the risk of hepatotoxicity when using 207 of the most commonly prescribed oral drugs [8]. It turned out that the use of drugs,

which are more than 50% metabolized in the liver, is significantly more often associated with an increase in the level of ALT more than 3 times compared to the upper limit of the norm, is more often accompanied by liver failure, the need for liver transplantation, and fatal consequences than the use of drugs with a less intense metabolism. When using 12 drugs that are not metabolized in the liver, including the antibiotics cefdinir, cephalexin, and cefuroxime, no cases of failure or need for liver transplantation, as well as fatal DILIs, were found.

In addition, there are data on the relationship between cytochrome P450 isoenzymes, which are involved in drug metabolism, and the development of DILIs. The latter are more often caused by drugs subject to biotransformation with the participation of CYP 2C9 and CYP 2C19 than CYP3A and CYP2D6. Some drugs can change the hepatotoxic potential of other drugs by inducing or inhibiting cytochrome P450 enzymes, which leads to the accumulation of toxic metabolites [13]. The strongest enzyme inducers are rifampicin and antiepileptic drugs, as well as alcohol and smoking. Suppression of liver enzymes can be caused by 14-membered macrolides (erythromycin, clarithromycin), antifungal agents and antiretroviral drugs from the group of protease inhibitors. A classic example of DILI that occurs against the background of such a drug interaction is hepatitis with the joint use of isoniazid and rifampicin [2,4]. When using a combination of two hepatotoxic drugs, the risk of DILI can increase 6 times. Penicillins cause mainly hepatocellular damage to the liver, although cases of cholestasis with ductopenia (atrophy of the bile ducts) have also been described with their use. Cholestatic hepatitis is more characteristic of semi-synthetic antistaphylococcal oxypenicillins (flucloxacillin, oxacillin). DILI occurs extremely rarely during treatment with ampicillin and rarely - during treatment with benzylpenicillin, phenoxymethylpenicillin and amoxicillin. According to Great Britain pharmacovigilance data the frequency of hepatotoxic reactions to amoxicillin fluctuates from 0.1-0.2 to 3.0 per 100,000 prescriptions [13].

Amoxicillin / clavulanate and flucloxacillin have the highest potential for hepatotoxicity among penicillins. The risk of hepatotoxicity when using amoxicillin / clavulanate is 5-9 times higher than that for amoxicillin, 13-23% of all detected antibiotic-induced liver injuries are associated with its use. In a large UK population-based case-control study, the adjusted odds ratio (OR) for hepatotoxicity with amoxicillin / clavulanate (compared with no antibacterial therapy) was 94.8 (95% CI 27.8-323.0). The main risk factors for the development of DILI during treatment with amoxicillin / clavulanate are age over 65 years, female sex, as well as long and repeated courses of treatment. In case of a combination of these risk factors frequency of acute DILI can reach 1 in 1000 patients. Amoxicillin /

clavulanate also is leading among antibiotics according to the frequency of hospitalizations associated with DILIs. Jaundice during application of amoxicillin / clavulanate develops with a frequency of 9.91 cases per 100,000 appointments. Clinical and morphological manifestations of DILI during treatment with amoxicillin / clavulanate, as noted above, depend on duration of treatment as well as on age - for young patients hepatocellular damage is more characteristic, while for the elderly - cholestatic or mixed [11,12]. Despite the fact that in majority of patients with liver damage caused by amoxicillin / clavulanate prognosis is good, unfavorable results (transplantation liver or death) according to the results of the prospective research can observed in 7% of patients [10]. Due to risk of hepatotoxicity primarily associated with clavulanic acid its maximum daily dose for adults and children over 12 years old is limited to 600 mg/day, for children under 12 years old - 10 mg/kg of bodyweight [13].

It is important to note that nutritional and herbal supplements can be potentially hepatotoxic too. The results of research in recent decades have shown that herbal supplements can cause liver damage: from a mild asymptomatic increase in the level of cytolytic enzymes to severe inflammatory and destructive processes and vascular lesions. Highest level of evidence regarding hepatotoxicity is established for wall germander (*Teucrium chamaedrys*), marsh mint (*Hedeoma pulegioides*), celandine (*Chelidonium*), kava kava (*Piper methysticum*), cleopagonus cluster (*Actaea racemosa*). The hepatotoxicity of the leaves of the creosote bush (*Larrea tridentata*), senna (*Cassia angustifolia*), water-alcohol extracts of green tea and Herbalife is also known [1].

It should be noted that in the case of drug-induced hepatotoxicity, specific treatment measures are not carried out in most cases. For the most part, with DILIs, spontaneous recovery occurs without the need for additional administration of specific drugs, and only symptomatic therapy is prescribed. Treatment tactics, first of all, should be aimed at stopping the use of the hepatotoxic drug. As for the specific treatment of such liver pathology, pharmacotherapy has different approaches and depends on the drug that caused liver damage. Thus, N - acetylcysteine is used (oral administration at a dose of 140 mg/kg for the first 3 days followed by 70 mg/kg every 4 hours for 3 days or an intravenous 21-hour regimen: infusion of 150 mg/kg for 1 hour with further administration of the drug in a dose of 50 mg/kg for 4 hours, then 100 mg/kg for next 16 hours) in early manifestations of hepatotoxicity caused by taking acetaminophen. L - carnitine is prescribed in case of liver damage by valproate. The recommended dose of L - carnitine is 100 mg/kg bodyweight (but less than 6 g

in total) intravenously for 30 minutes, followed by 15 mg/kg every 4 hours until clinical improvement.

Correction of long-term drug-induced cholestasis is similar to management of primary biliary cirrhosis. In particular, to reduce itching, cholestyramine is used (in a dose of 4 g every 6 hours). It is also advisable to prescribe ursodeoxycholic acid 10-15 mg per kg bodyweight 2-3 times a day for this category of patients, the effectiveness of which has been proven in many clinical studies.

Corticosteroids are used for the autoimmune-like phenotype of DILI. Most often, this DILI phenotype is caused by drugs of the class of TNF inhibitors. The recommended dose of methylprednisolone is 20-40 mg per day, followed by a gradual reduction of the dose after the normalization of biochemical parameters within 6 months.

Ademethionine exhibits antifibrotic, antineurotoxic and antidepressant properties. There are data on the effectiveness of ademethionine in the treatment of cholestatic forms of DILI caused by the use of methotrexate, cyclosporine and corticosteroids in patients with severe degree of psoriasis. The recommended regimen of ademetionine: 1000 mg per day intravenously for 2 weeks, then 1000-1500 mg per day orally for 1 month.

No less important in the treatment of drug hepatotoxicity is the use of other hepatoprotectors. These are drugs, the action of which is aimed at increasing the resistance of hepatocytes to the action of pathogenic factors, normalizing functional activity and stimulating reparative and regenerative processes in the body. To date, the effectiveness of many hepatoprotectors has been partly established, including arginine glutamate/citrate, Fumaria officinalis, Silybum Marianum, betaine, glutathione, essential phospholipids, antral [8].

Prevention of DILI should include a detailed anamnesis before the use of drug therapy, personalized identification of associated risk factors in specific patients. It is important to avoid polypharmacy in order to exclude drug interactions. If potentially hepatotoxic drugs are prescribed, laboratory parameters of cytolysis and cholestasis should be monitored. To prevent DILI, it is advisable to use drugs with a high safety profile. In the case of prescribing drugs with potentially high hepatotoxicity, it is often necessary to carry out genetic tests for individual sensitivity, such as determination of polymorphism of genes of biotransformation systems.

Conclusions. Hepatotoxicity of drugs remains one of the urgent problems of modern medicine, as it leads to a decrease in the effectiveness of pharmacotherapy, development of serious complications that can cause disability and death. Such a side effect increases the

length of stay of patients in the hospital and increases the cost of treatment. That is, the problem of hepatotoxicity is not only a medical, but also a social problem.

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