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Risk Factors, The Main Mechanisms and Clinical Variants of Liver Damage. Principles of Diagnosis and Treatment of Medicinal Liver Lesions

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ABSTRACT: The article presents current data on the problem of medicinal liver damage and a number of clinical observations of the author. The risk factors, main mechanisms and clinical variants of liver damage, as well as the principles of diagnosis and treatment of drug-induced liver damage are indicated.There isno strong correlation between the severity of changes in the biochemical parameters of liver damage and clinical symptoms, a high risk of coagulopathy, and the need for long-term multicomponent monitoring of liver function and hemostasis.

KEYWORDS: drug-induced liver diseases, mechanisms, clinical variants, diagnostics principles, treatment

In recent decades, there has been an increase in the number of side effects and complications of drug therapy worldwide, most of which are drug-induced liver damage (LPP) [1]. To a large extent, this is due to the liberalization of public access to medicines, as well as aggressive advertising activities of some pharmaceutical manufacturers and their representatives. [2]. This resulted in an increase in the number of LPS in various categories of patientsIt is well known that any drug (drug), herbal preparation or dietary supplement (BAA) can lead to the development of LPP. However, the most common causes of LPP are hormonal contraceptives, anabolic steroids, antibacterial drugs (especially amoxicillin/clavulanate, ceftriaxone, clarithromycin, azithromycin, tetracyclines, aminosalicylates, and fluoroquinolones), nonsteroidal anti-inflammatory drugs (NSAIDs) (most often paracetamol and diclofenac), systemic antifungal and anti-tuberculosis drugs [2-6]. The literature describes cases of LPP development with the use of large celandine, licorice, Alexandrian leaf, Dubrovnik, comfrey, marsh mint, skullcap, pyrrolizidine alkaloids, chaparral, [6].It is believed that in medical practice, LPP occurs with a frequency of at least 1 case per 1000 treated patients, accounting for 10% of all adverse drug reactions [1, 7]. However, the true prevalence of LPP appears to be significantly higher. It is enough to mention that 40% of all cases of diagnosed hepatitis are caused by drugs, and among patients over the age of 40, more than 50% of cases of hepatitis are drug-induced [8]. A significant part of non-specified etiology of hepatitis and cirrhosis of the liver is also a manifestation of LPP.

Risk factors for the development of LPP are extremely diverse [9-13].

- Potential hepatotoxicity of drugs.
- The drug dose used.
- Polypragmasia (for example, when taking 6 drugs, the probability of LPP reaches 80%).
- Irrational combinations of drugs that cause 35% of LPP.
- Genetic predisposition to LPP due to differences in the activity of liver enzymes that metabolize drugs.
- Gender and age of the patient. More often, LPP occurs in women, as well as in people over 50 years of age, since the elderly slow down the excretion of drugs from the body due to a decrease in blood flow in the liver and the activity of drug-inactivating enzymes. Children rarely develop LPP. There is a certain specificity of the development of LPP in various categories of patients. In particular, in postmenopausal women, the liver is particularly sensitive to NSAIDs, in young patients — to paracetamol and aspirin, in the elderly-to anti-tuberculosis drugs, nitrofurans and antibiotics.

Liver pathology [14]: steatosis, hereditary hepatoses, liver damage caused by hepatotropic viruses (hepatitis B, C viruses, cytomegalovirus, Epstein – barr viruses -Barr, herpes simplex, etc.), the presence of liver failure or cholestasis, which contributes to the accumulation of drugs and their metabolites in the liver.

Severe diseases of the cardiovascular, respiratory, endocrine systems and kidneys, accompanied by severe dysfunction of the affected organs.

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- Underwent cardiac surgery with artificial blood circulation, which contributes ишемизациито the ischemia of liver tissue.
- Alcohol.
- Poor animal protein diet, especially combined with hypoalbuminemia, which changes the kinetics of drugs. This risk factor is especially important for patients who abuse alcohol, people who adhere to all kinds of restrictive diets (vegetarianism, etc.) or strictly observe religious fasts.

Cytolytic NSAIDs, antiarrhythmics, statins, cytostatics, and antibacterial drugs have a cytolytic effect т.ч. anti-tuberculosis drugs). The cholestatic effect is most often provided by oral contraceptives, anabolic steroids, ceftriaxone, fibrates, anticonvulsants, and antidepressants. Mixed forms of direct hepatotoxic reactions are observed with the use of NSAIDs, aspirin, nicotinic acid, aminosalicylates, sulfonamides, quinidine, allopurinol, valproic acid and antitumor drugs.

To build an adequate treatment strategy, it is important to identify variants of direct hepatotoxic effects of drugs based on standard biochemical criteria [9]:

Cytolytic variant: ALT≥5N, ALT / ALP≥5; increased lactate dehydrogenase(LDH), serum iron, ferritin and bilirubin (mainly direct fraction).

- Cholestatic variant: ALP≥2N, ALT/ALP<2; increased GGTP, cholesterol, bilirubin (mainly direct fraction), bile acids in the blood.
- Mixed variant: ALT≥2N, ALP≥2N, 5≤ALT/ALP≥2; increased GGTP, cholesterol, bilirubin (mainly direct fraction), as well as signs of mesenchymal-inflammatory syndrome (increased ESR, CRP, gamma-globulins).

Immunoallergic LPPs are characterized by liver damage due to allergic reactions to drugs of the delayed hypersensitivity type. It is characterized by granulomatous liver damage in combination with systemic manifestations. They usually develop after 2-4 weeks of treatment with NSAIDs, antithyroiddrugs, anticonvulsants, and quinine preparations. The extreme variety of LPP mechanisms determines the versatility of their clinical variants (hepatopathies) [8]. To date , drug-induced steatosis and steatohepatitis, acute and chronic drug-induced hepatitis , mitochondrial cytopathies, drug-induced liver fibrosis , drug-induced cholestasis, drug-induced sclerosing cholangitis , phospholipidosis, liver vascular damage, liver damage by type of hypersensitivity reactions , hepatocyte necrosis, fulminant hepatitis have been described. [10].

Drugc-induced liver steatosis is associated with amiodarone, synthetic estrogens, calcium antagonists, antimalarials, tetracycline, NSAIDs, glucocorticoids, valproic acid, and antitumor drugs. Drugстеатоз-induced liver steatosis is clinically heterogeneous-from an asymptomatic increase in transaminases to acute fatty liver disease, which develops in 2-6% of cases. [5].

Hepatocellular necrosis can be the result of direct toxic effects of drugs (most often paracetamol, salicylates, cocaine, as well as iron preparations when taken orally in large doses) or idiosyncrasy. Its features are, firstly, the development of fulminant liver failure (described with the use of more than 40 drugs, including paracetamol, ketoprofen, nimesulide and clarithromycin), and secondly, frequent damage to other organs and systems (acute gastritis, enteritis, acute renal failure, etc.). [10].

Drug-induced liver damage such as a delayed hypersensitivity reaction usually develops after 2-4 weeks of treatment, especially with repeated administration of NSAIDs , thyrostatics, quinine preparations, anticonvulsants and sulfonamides. Allergic hepatitis is often associated with fever, rash, arthritis, cutaneous vasculitis, eosinophilia, hemolysis (DRESS syndrome). Both hepatocellular and cholestatic liver damage can develop. [13]. At the same time, clinically, there is a large variability of manifestations: from isolated acute hepatitis of moderate activity to active hepatitis with various systemic lesions.

Treatment of LPP in all categories of patients includes the elimination of the drug that caused LPP, recommendations for therapeutic nutrition (protein content of at least 60-100 g /day, restrictions corresponding to the 5th table according to Pevsner), and the appointment of drugs that allow limiting LPP. [1,15].

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In conclusion, I would like to note that the problem of LPP and other manifestations of adverse reactions of drug therapy should be widely discussed at various levels, including: from the perspective of optimizing the interaction of the doctor, patient, pharmaceutical worker, pharmaceutical companies and their representatives, interested ministries and departments. In the framework of this article, it should be emphasized that when prescribing drug therapy, especially long-term, with the use of several drugs, drugs that can potentially cause LPP, to ensure the safety of patients, the state of liver functions should be periodically evaluated, paying special attention to the biochemical criteria of LPP.

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