DRUG-INDUCED LIVER DAMAGE

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Abstract: *Drug-induced liver damage (DILD) is a heterogeneous group of clinical and morphological variants of liver damage against the background of medication administration for medical indications in usual therapeutic doses due to both direct toxic (usually predictable) and toxic-immunologic (idiosyncratic) or allergic types of effects. The spectrum of clinical manifestations of drug-induced liver disease is extremely diverse; these manifestations often have similarities to "classical" forms of liver disease. The basis of diagnosis is a carefully collected anamnesis about the drugs used.*

In case of prolonged intake of hepatotoxic medicines with moderate degree of liver damage it is advisable to take hepatoprotective agents from the very beginning of drug therapy. In most cases for prevention of LPT (simultaneously from the first day of taking a drug with known hepatopoisoning effect) or for treatment of diagnosed LPT of moderate and mild severity it is enough to take hepatoprotective silymarin-containing drug with high bioavailability, inhibiting the processes of fibrogenesis, contributing to the restoration of hepatoprotective liver disease. Key words: drug-induced liver damage, hepatoprotectors. In recent years, the importance of drug-induced liver damage (DILD) has increased significantly, and this problem is faced by doctors of all specialties. The difficulty in diagnosing DLD lies in the fact that clinical and laboratory manifestations and histologic features may "simulate" other liver diseases or overlap with existing viral and/or alcoholic liver damage. At the same time, LPP should be diagnosed at an earlier stage, because the continued use of drugs can repeatedly increase the severity of clinical manifestations and significantly affect the outcome of the disease as a whole. According to A.O. Bueverov [1], "the true prevalence of drug-induced liver damage remains and, apparently, will remain unknown, but it can be stated that in clinical practice this diagnosis is formulated unjustifiably rare. This is due to several factors, among which the most important are: 1) reluctance of the patient to report taking certain drugs (antidepressants, neuroleptics, etc.); 2) reluctance of physicians to document iatrogenic diseases.

General factors predisposing to the occurrence of LPP are as follows: 1) prescription of drugs in high doses; 2) drug dosing without taking into account individual characteristics of the patient; 3) prolonged treatment; 4) polypragmasia; 5) liver diseases of any etiology; 6) background systemic diseases (especially renal diseases). Zimmerman in 1978 proposed to refer substances causing liver damage to one of 2 groups: 1) obligate hepatotoxicants and 2) damaging the organ only in sensitive individuals (idiosyncratic) [2]. Obligate hepatotoxicants cause a predictable dose-dependent effect, usually reproducible in

experiments on experimental animals. In a small proportion of people, drugs that do not exhibit the properties of hepatotoxicants in experiment, nevertheless cause liver damage. The phenomenon is based on genetically determined features of metabolism of xenobiotics and other causes of increased susceptibility of the organism to the drug substance. This type of pathology is not reproduced in experiment and is not dose-dependent. The criteria allowing to distinguish between these forms are presented in Table 1. In practice, however, it is not always possible to clearly distinguish between direct hepatotoxicity and idiosyncrasy. Moreover, in susceptible patients, some drug compounds previously classified as allergens appear to directly damage hepatocyte membranes through intermediate toxic metabolites.

Table 1: Toxic and idiosyncratic liver lesions in drug exposure

Parameters	Toxic liver damage	Idiosyncratic liver damage
Predictability	yes	no
Dose dependence	yes	no
Reproducibility in experimental animals	yes	no
Damage to other organs	Perhaps	Very rarely
The underlying pathogenetic mechanism	Dose-dependent formation of toxic metabolites	Immune disorders
Examples of drugs by main hepatotoxic effect	Paracetamol, aspirin, tetracyclines, griseofulvin, amiodarone, estrogens, anabolic hormones, mercaptopurine, methotrexate, semisynthetic penicillins, cytostatic antibiotics	Эритромицин, изониазид, галотан, хлорпромазин

The toxic substance may directly affect the structure of the hepatocyte (paracetamol metabolite N-acetyl-p-benzoquinone) and/or have an indirect effect on specific metabolic reactions (e.g. inhibition of protein synthesis in cytostatic antibiotics). Most direct hepatotoxicants cause dose-dependent liver necrosis, often in the presence of effects on other organs (kidneys). The classic drug with an obligate hepatotoxic effect is paracetamol. The basis of the toxic effect of drugs on the liver is damage to hepatocytes. The mechanisms underlying the hepatocytotoxic action of drugs (Table 2) are closely related to each other, often aggravating the effect of each other by the type of "vicious circle".

Table 2. Main mechanisms underlying the hepatotoxic effect of drugs

Immune mechanisms	Physicochemical mechanisms
Formation of neoantigens and autoantibodies; functioning of killer lymphocytes; synthesis of anti-inflammatory cytokines; activation of the complement system	Activation of free radical processes. Damage to plasma and cytoplasmic membranes. Disruption of mitochondrial function. Disturbance of intracellular ionic homeostasis. Disaggregation of ribosomes and endoplasmic reticulum

The spectrum of clinical manifestations of drug-induced liver disease can be extremely diverse, but acute hepatitis-type lesions are the most common (approximately

80% of cases). Chronic LDL can be an independent disease (e.g., with long-term administration of methyldopha), but usually develops as an outcome of an acute pathologic process (with prolonged intake of drugs or their combination). The severity of the course of drug-induced liver disease varies from asymptomatic elevation of transaminase levels to the development of fulminant liver failure (FLF).

In addition to the symptoms characteristic of liver disease (jaundice, skin itching, "liver signs," bleeding, liver enlargement, and pain on palpation), generalized manifestations (nausea, abdominal discomfort, decreased appetite, general weakness, and decreased ability to work) are common. Although the development of acute liver failure is possible, nevertheless, in most cases drug reactions are transient and resolve spontaneously.

The latency period with hepatotoxic dose-dependent drugs is usually short (pathologic manifestations develop within 48 h from the start of administration). Depending on the degree of increase in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels, acute liver injury is classified as hepatocellular (cytolytic), cholestatic or mixed, combining signs of cholestasis and cytolysis (Table 3).

Table 3: Main types of acute drug-induced liver injury

Type of lesion	Alanine amino transferase (ALT)	Alkaline phosphatase (APh)	ALT/APh ratio
Cytolytic	>2	norm	High (>5)
Cholestatic	norm	>2	Low (<2)
Mixed	>2	>2	2-5

In case of cytolytic type of liver damage, drug withdrawal leads to improvement of biochemical parameters within 2 weeks on average, whereas in case of cholestatic or mixed types of liver damage positive dynamics can be absent within 4 weeks. Biochemical shifts, existing for a longer time, suggests the presence of concomitant liver disease or other etiology of existing disorders (viral, autoimmune hepatitis, primary biliary cirrhosis, etc. More often, in 2/3 of cases, there is a hepatocellular type of damage. An increase in ALT activity up to 5 times the upper limit of normal is considered as moderate hyperfermentemia; 6-10 times - as hyperfermentemia of medium degree, more than 10 times - as high. In drug-induced liver diseases, elevation of ALT level is the most sensitive test of early diagnosis. In mitochondrial hepatocytopathies, aspartate aminotransferase (AST) activity is significantly increased. Depending on the underlying type of liver damage, clinical symptoms and changes in biochemical parameters can vary widely.

Acute drug-induced hepatitis of varying severity is probably the most common drug-induced liver injury. As a rule, it is caused by idiosyncrasy reactions, the risk of drug hepatitis increases with prolonged and repeated use of the drug. The clinical picture in the prodromal period is dominated by dyspeptic disorders, asthenic, allergic syndromes. With the development of jaundice period darkening of urine and lightening of feces are noted, liver enlargement and painfulness are detected. Increased aminotransferase activity and

alkaline phosphate levels are in direct correlation with cytolysis and spread of liver necrosis. The level of γ-globulins in serum is increased. With the withdrawal of the drug regression of clinical symptoms occurs quite quickly. In some cases, drug-induced hepatitis carries a risk of fulminant hepatic failure, the mortality rate of which can reach 70%. Acute drug-induced hepatitis has been described with the administration of antituberculosis agents (especially isoniazid), aminoglycosides (streptomycin, amikacin, rifampicin), hypotensive drugs (methyldopa, atenolol, metoprolol, labetalol, acebutolol, enalapril, verapamil), antifungal agents (ketoconazole, fluconazole), antiandrogenic drugs (flutamide), tacrine (reversible cholinesterase inhibitor used in Alzheimer's disease), clonazepam (anticonvulsant) [3, 4].

Steatohepatitis. Corticosteroids, tamoxifen and estrogens may act as "trigger" factors for steatohepatitis in predisposed individuals, such as those with diabetes, central obesity or hypertriglyceridemia. Drug-induced steatohepatitis usually develops on the background of long-term pharmacotherapy (more than 6 months) and seems to be associated with drug cumulation. Acute fatty changes in the liver can cause tetracyclines, NSAIDs, as well as corticosteroids, valproic acid and anticancer drugs. A feature of steatohepatitis caused by some drugs is its continued progression after drug withdrawal.

Chronic drug-induced hepatitis can also be caused by repeated administration of nitrofurans for recurrent urinary infection, clomethacin, fenofibrate (hypolipidemic drug), isoniazid (tuberculostatic), papaverine, minocycline (a tetracycline antibiotic), and dantrolene (a muscle relaxant used to relieve muscle spasms in cerebral palsy, multiple sclerosis, and spinal cord injury). Chronic drug-induced hepatitis more often develops in persons who chronically consume alcohol. Acute cholestasis has been described in the use of drugs of different pharmacological groups, including. estrogens, anabolic steroids, tamoxifen, neuroleptics (chlorpromazine), statins, antibiotics (erythromycin, oxypenicillins, fluoroquinolones, amoxicillin/clavulanate), antiaggregants (ticlopidine), antihistamines (terfenadine) and antifungals (terbinafine), NSAIDs (nimesulide, ibuprofen), hypotensive (irbersartan) and antiarrhythmic drugs (propafenone) etc.

Isolated hepatocellular cholestasis is more often observed with the use of sex hormones and anabolic steroids. Drug-induced cholangiopathy (cholestasis in small or interval ducts) can be acute and selfresolved after drug withdrawal or, on the contrary, take a protracted course, leading to ductopenia and sometimes biliary cirrhosis.

Diagnosis of drug-induced liver lesions Early diagnosis of LDL is of particular importance because of the high risk of disease progression without drug withdrawal. The possibility of such lesions is taken into account when liver function is impaired in patients taking various drugs and alternative medicine products. Due to the large number of asymptomatic drug-associated liver diseases in patients receiving hepatotoxic drugs, and in case of polypragmasia, it is advisable to regularly (at least once every 2 weeks, and in case of long-term therapy - once a month) determine the activity of aminotransferases, alkaline phosphatase and bilirubin level in serum. If transaminase activity is increased more than 3

times, the drug is canceled. An alternative to drug withdrawal, and if it is necessary to continue treatment with a hepatotoxic drug, is to reduce the dose of hepatotoxicant with the administration of an oral hepatoprotector. The drug of choice in this situation is silymarin-based drugs. Indication for immediate withdrawal of the drug - the appearance of fever, rash or pruritus in the patient. The basis of diagnosis of LPP is a carefully collected history of the drugs used with an assessment of the duration and dose of the drugs received, finding out the possibility of their use in the past. It is necessary to clarify the immediate anamnesis, to find out whether there was no intake of biologically active food supplements. They are not formally medicines, but they are usually positioned as means of treatment of a wide range of diseases, including liver diseases, and the substances included in such products often have pronounced hepatotoxic properties (Table 4).

Table 4: Medicinal plants with potential hepatotoxic effects

Plant	Possible side effect	Active ingredient
Alexandria leaf	hepatitis	senoside
Valeriana	hepatitis	Alkylating agents
Dubrovnik	hepatitis, cirrhosis	flavanoids
Green tea	hepatitis	catechin
Dwarf oak	hepatitis	Organic acids
Kambucha (tea mushroom)	hepatitis	unknown
Melissa marsh	Liver necrosis	pulegon
Bog mint	Liver necrosis	pulegon
Comfrey	Veno-occlusive disease, adenoma, cirrhosis	Pyrrolizidine alkaloids
Mistletoe	hepatitis	unknown
Sassafras	hepatitis, liver cancer	sarfrole
Stemwort	hepatitis	unknown
Chameleon white	hepatitis	unknown
Cilantro	hepatitis	unknown
Clematis	necrosis	glycosides

The diagnosis of drug-associated liver lesions is in most cases a diagnosis of exclusion. A variant of the diagnostic algorithm is presented in Table 5.

Table 5: Scope of diagnostic tests for suspected drug-induced liver disease

Stage I (polyclinic: district therapist, gastro-enterologist of the polyclinic)	**Stage II (inpatient: therapeutic or gastroenterology departments)**	**Stage III (hepatology center)**
Study of chronology of development and regression of symptoms of the disease General clinical analysis of blood, urine Biochemical analysis of blood (in dynamics) AST, ALT, alkaline phosphate, bilirubin, GGTP, total protein, glucose, cholesterol Prothrombin index Ultrasound of abdominal cavity EGDS HbSAg, anti HCV Chest X-ray	Thorough drug history Biochemical blood analysis: dynamics of markers of cytolysis and cholestasis, total protein, albumin, glucose, cholinesterase, iron Serum protein electrophoresis Immunoglobulins Abdominal CT Colonoscopy (in case of cholestasis) ERCG (in case of cholestasis) Liver Biopsy	Markers of viruses causing hepatitis Serum ceruloplasmin, daily excretion of copper with urine Transferrin carbohydrate-deficient Antibodies: ANA, SMA, LKM-1, p-ANCA Doppler scan of liver vessels Liver biopsy

With the help of biochemical and immunologic studies, ultrasonography (and in some cases other methods of radiation diagnostics) liver diseases of other etiology are established. But it should be remembered that LPP can overlap with "classical" liver disease and change its course. Attempted repeated exposure to the drug substance is unacceptable for ethical reasons. The diagnosis is confirmed if clinical symptoms, changes in biochemical parameters and histologic signs of liver damage disappear or diminish after discontinuation of the drug. Liver biopsy may be indicated if there is suspicion of previous liver pathology or if biochemical parameters do not normalize after drug withdrawal. There are no specific histologic changes for LPP. Granulomas, a significant admixture of eosinophils in the inflammatory infiltrate, a clear zone of delineation between the area of necrosis and unaffected parenchyma are often found. In clinical and morphologic comparisons, the discrepancy between the severity and volume of morphologic changes and the overall relatively satisfactory condition of the patient and moderate shifts in liver test parameters draws attention.

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