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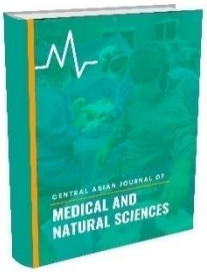

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Drug-Induced Damage to Liver Cell Structure

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Abstract: The liver, which is the largest gland of the human body, has a tremendous biological activity, playing a leading role in at least 11 important biochemical processes and taking a significant part in 60-70 more. Given this, it is evident that drug damage to the organ, which is involved in many pathological processes, causes serious disturbances in metabolism, immune response, detoxification and antimicrobial protection.

Keywords: hepatotoxicity, drug-induced liver injury (DILI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), rheumatoid arthritis, drugs.

Relevance. LBP occurs at a frequency ranging from one per 1,000 patients to one per 100,000 patients who take drugs at therapeutic doses. There are currently more than 1,000 registered drugs that have the potential to cause liver damage (26).

The World Health Organization's (WHO) VigiBase global database of suspected adverse drug reactions for 2016 contains 13,208,000 reports. During 2015-2016 alone, it increased by 18% (1.984 million new cases) [18, 22].

One of the most common side-effects associated with the administration of medicines (drugs) is hepatotoxicity. Drug-induced liver injury (DALI) accounts for about 10% of all adverse reactions caused by the use of pharmacological agents; its high prevalence, wide range of clinical manifestations, lack of unambiguous diagnostic methods, and often poor prognosis make DALI one of the most difficult problems in clinical practice. It should be noted that liver lesions can be caused not only by FPP, but also by dietary supplements and herbal remedies. For the sake of convenience they are all grouped by the term PDA [7, 22]. The most frequent PDA are observed when using antibacterial drugs (including antituberculosis, antifungal), analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy drugs, anti-epileptics, some groups of cardiovascular drugs, immunosuppressants (azathioprine), and separately should be marked BAS and phytopreparation [3,5].

Many drugs are potentially hepatotoxic. The number of drugs that cause liver damage increases every year: 748 surfactants were reported in 1991, 808 in 1992, and about 1000 surfactants by the beginning of 2000. - There are about 1000, and the list of these drugs is constantly growing [2,6]. At present, liver damage, from subclinical forms to fulminant liver failure, has been described for about 1000 drugs. Of the millions of known chemicals, more than 63,000 are widely used, of which about 55,000

compounds are drugs that pose a risk to humans [6,11]. The incidence of DTP depends largely on the number of concomitant medications. Thus, in case of concomitant use of 5 drugs, liver dysfunction occurs in 4%, in case of taking 5-10 drugs - in 10%, in case of using 10-16 drugs - in 28%, and in case of taking more than 16 drugs, the expected incidence of liver damage is 60% and more [2,7]. In recent years, there has been a clear upward trend in the number of LTBIs due to the continuous expansion of the pharmaceutical market. In Japan, for example, there has been an 11-fold increase in drug HT over a 30-year period.

The main reasons for the current increase in the incidence of STDs are broad public access to medical information and mass self-medication, an increase in over-the-counter medicines, the rapid development of the pharmaceutical industry (for example, in Russia alone about 1500 new medicines are registered annually), the increasing share of unlicensed generics in the pharmaceutical market, late identification of hepatotoxic effects in new drugs in different age and national population groups, and the ageing of the population.

According to recent epidemiological data, there are about 20 new cases of PLP per 100,000 people annually [9].The problem is that PLP, being a frequently encountered pathology, is still a rarely diagnosed disease, is characterized by non-specific and diverse manifestations, can occur as an unpredictable or inherent lesion as a result of using hundreds of drugs. This is associated with diagnostic difficulties, untimely withdrawal of drugs with hepatotoxic effects, and severe consequences for the patient. Different drugs can cause the same type of liver damage, and the same drug can cause liver damage with different clinical manifestations.

Direct adverse drug effects on liver cells, toxic effects of drug metabolites (DMs) and immunoallergic organ damage are the leading causes of drug-induced liver injury (LD injury)[3,13].

A distinction is made between predictable, dose-dependent (e.g. in the case of paracetamol) and unpredictable/idiosyncratic hepatotoxicity of drugs. The latter, may occur with immunoallergic and/or metabolic idiosyncrasic reactions and be supported by the innate and adaptive immune system. Idiosyncrasic LPS is relatively rare, with an estimated incidence of 14-19 cases per 100,000 people.

Idiosyncratic liver damage comes in different forms (acute and chronic hepatitis) and can have different, including severe, consequences: in 2-4% of cases patients need liver transplantation and in 8-10% the severe course of LPT leads to lethal outcome. In 13-18% of cases, LPT can progress to chronic liver damage and cirrhosis.

Knowledge of risk factors allows not only the prediction of LTBI, but also the monitoring of clinical and laboratory parameters for timely decision on measures in the development of hepatotoxicity. The risk factors of LBP are constantly being specified. They can be divided into 3 groups: patient-related factors; drug-related factors; and additional (external) factors (Fig. 1). Risk factors related to LP include the dose of the LP, its lipophilicity, and the degree of metabolism in the liver. On the patient side, risk factors such as age, gender, ethnicity, and pre-existing chronic liver disease are considered (32). [32]. Genetic and immunological factors are of particular importance in the pathogenesis of LTBI. In some cases, a patient's genetic predisposition may be a risk factor for the development of LTBI.

The main risk factors for the development of LTBI are

- Over 40 years of age
- Female gender
- genetic predisposition

- Taking 5 or more drugs
- Taking combinations of drugs with potential hepatotoxic effects (antibiotics, anti-inflammatory drugs, calcium antagonists, amiodarone, antidepressants, anticonvulsants, iron, nicotinic acid, H2-histaminoblockers, anabolic steroids, synthetic oestrogens, cytostatics, TB drugs, antifungals, etc.)
- longer duration of high doses of the drug over 3 months
- History of drug reactions
- alcohol use
- comorbid cardiovascular, renal (cardiac, renal failure) disease
- the presence of underlying liver damage (steatosis, steatohepatitis, viral hepatitis, etc.)
- the presence of systemic, autoimmune disease
- protein malnutrition
- Obesity, cachexia

Recent genome-wide association studies (GWAS) have found strong associations between different polynucleotides in the HLA histocompatibility gene region and individual susceptibility to the development of LTBI [32]. Smoking can induce cytochrome P450 (CYP) enzymes, but this does not necessarily lead to LTBI. Alcohol consumption is a risk factor for hepatotoxicity and may predispose to LPP. The significance of infectious factors, pro-inflammatory conditions, and microbiome conditions as risk factors for LTP is still under investigation [4, 14]. **Factors influencing the development of LPP**

External factors	Internal factors	Factors related to the medicinal substance
Alcohol, coffee, tobacco, microbiome, toxins, viruses	Gender, age, disease, genetics, immune status, metabolism	Structure, molecular weight, lipophilicity, dose, duration of therapy
External factors	Genetic factors(drug metabolism, detoxification, transport)	Toxic potential of drug substance

One of the most common somatic pathologies in the treatment of which liver damage develops is rheumatic disease. This may be due to several factors. Firstly, the administration of drugs for the treatment of rheumatic diseases is always long and sometimes lifelong, and often high dosages are used, secondly, patients of rheumatological hospitals are women in 80% of cases, and it is women who are more susceptible to hepatotoxic effects [2,8].

We would like to dwell on the basic groups of medicines used in treatment of rheumatic diseases:

- NSAIDS. Asymptomatic elevations in transaminase levels are noted in 5-15% of patients who regularly take NSAIDs. The occurrence of TDBP due to taking NSAIDs can occur at different times: immediately after the start of treatment, weeks or even months after the end of treatment, more often between 6-12 weeks from the start of therapy. PSTs most commonly develop with nimesulide, diclofenac, less frequently with naproxen, indomethacin, ketorolac, meloxicam [1,7,9].

- Methotrexate. The most common side effect of methotrexate use is a transient increase in liver enzymes. Liver fibrosis is also known to occur with long-term treatment with methotrexate. Risk factors for LLLT with methotrexate include age, high dose, lack of folic acid intake, alcohol consumption, obesity, diabetes, underlying liver disease, and psoriasis. Transaminase monitoring is considered sufficient as a reliable marker of liver damage

Leflunomide. There are studies confirming the lesser hepatotoxicity of leflunomide compared to methotrexate. The most common is a dose-dependent increase in transaminases. Manufacturers now recommend that alanine aminotransferase (ALT) levels be tested before starting treatment, then once or twice a month for six months, and every 6-8 weeks thereafter.

- Azathioprine. Complications during its administration are rare, but often have a severe course. They include cholestatic hepatitis, hepatic vascular disease (peliosis, portal hypertension) .
- Cyclosporine. Cases of moderate cholestasis, which is usually reversible, have been described.
- Cyclophosphamide. Some cases of parenchymatous liver damage and steatosis have been associated with its administration [1, 11].
- Tumour necrosis factor inhibitors a. According to some authors, the risk of hepatotoxic reactions during treatment with tumor necrosis factor a inhibitors is minimal, and most cases are described against infliximab. On the liver side, cases of elevated transaminases have been described, but more severe manifestations, including autoimmune hepatitis, cholestasis and liver failure, have also been reported.
- Glucocorticosteroids. The ulcerogenic effects of glucocorticosteroids are widely known. However, plasma transaminase and alkaline phosphatase (ALP) activity may increase after glucocorticosteroid treatment. However, these changes are usually mild and are not associated with any clinical syndrome.

After discontinuation of treatment, a normalization of the indexes is observed.

In clinical practice, the diagnosis of drug-induced liver injury is unjustifiably rare, as the true prevalence is difficult to assess. This is due: on the one hand, to the frequent concealment of side effects of drugs by physicians; on the other hand, to the lack of awareness of their clinical manifestations. Clinical manifestations of LPS can range from no or mild symptoms with minor abnormalities in laboratory tests (most often a slight increase in aminotransferases) to severe cytolytic and cholestatic syndromes with jaundice and even acute liver failure with hepatic coma and death. In a mild course of the disease, there is a rapid reversal of the process if the drug is withdrawn.

LPT has no well-defined, disease-specific clinical manifestations, but its spectrum encompasses symptoms found in a variety of liver lesions, from asymptomatic elevated transaminases to the development of FAP. Moreover, the same drug can cause different clinical and morphological variants of LTP, but acute hepatitis-like lesions predominate. Chronic LBP can occur not only as a primary disease but also as an outgrowth of an acute process. Acute cholestasis is not uncommon, particularly with estrogens, anabolic steroids, antibiotics and some other drugs [4, 6, 10].

Acute drug-induced hepatitis is probably the most common ARF. Acute drug-induced hepatitis has been described with anti-TB agents (especially isoniazid), aminoglycosides (streptomycin, amikacin, rifampicin), antihypertensive drugs (methyldopa, atenolol, metoprolol, enalapril, verapamil), antifungals (ketoconazole, fluconazole), antiandrogens (flutamide), tacrine, pemoline, clonazepam

[2,5]. The likelihood of developing drug-induced hepatitis increases with prolonged and repeated drug administration.

Dyspeptic disorders, asthenic and allergic syndromes are noted at the beginning of the disease. Patients complain of weakness, discomfort in the epigastrium and right subcostal area, worsening of appetite, nausea and, rarely, vomiting. Along with the development of jaundice, there is darkening of the urine and clarification of the stool. The cholestatic variant may be accompanied by persistent itching of the skin.

There is pain in the right subcostal area, and the liver is enlarged and painful.

Laboratory examination reveals increased levels of both indirect and direct bilirubin, with the latter usually predominating, especially in cholestasis. Elevated aminotransferase activity reflects the severity of the cytolytic syndrome, as well as the levels of TSH and g-glutamyl transpeptidase, indicating the development of intrahepatic cholestasis. Serum g-globulin levels may increase. With a favourable course and abolition of the drug, the reversal of clinical symptoms is rapid .

The main biomarkers used for LPS typing are ALT and alkaline phosphate levels, which reflect the balance between cytolytic and cholestatic processes. Three types of acute LPS can be distinguished (see table), with hepatocellular damage being more common. The severity of the cytolytic process is also usually characterized by ALT activity: an increase of 1.5-5-fold over the upper limit of normal is regarded as mild hyperfermentemia, 6-10-fold as moderate hyperfermentemia, and more than 10-fold as high .

PAF is a clinical symptom characterized by the sudden development of severe liver dysfunction, manifested by encephalopathy, marked hypocoagulation and other metabolic disorders. PAD can be caused by anaesthetics, NSAIDs, antidepressants and isoniazid in combination with rifampicin. The occurrence of this condition is possible with an acute overdose of paracetamol. The hepatotoxicity of this drug is directly related to its pharmacokinetics. In the medium therapeutic dose range, paracetamol is mostly transformed by the formation of conjugates with iglucuronide sulphate. About 5-10% of paracetamol is metabolised in the cytochrome P450 system to form the toxic metabolite N-acetyl-parabenzoquinomine, whose toxicity is eliminated by glutathione, and is then excreted in the urine or bile. The unconjugated part of the metabolite may bind to various structures of the hepatocyte and cause cellular damage.

Types of acute LPP			
Type of lesion	ALT	ALKALINE PHOSPHATE	**ALT/ABP ratio**
Hepatocellular	>2	norm	>5
Cholestatic	Norm	>2	<2
Mixed	>2	>2	2-5

There may be telangiectases in the skin and erythema pallidum on the palms. Biochemical tests show increased bilirubin, transaminases, alkaline phosphate, decreased prothrombin index, albumin, etc. Retention of these symptoms for 3 months is convincing evidence of the formation of chronic medicinal hepatitis.In other cases, gradual development of the disease, long-term maintenance of dyspeptic and asthenic syndromes are possible. Subicteric sclerosis, heaviness in the right subcostal area, increased transaminase and alkaline phosphatase activity may occur. With continued use of the drug that caused hepatitis, symptoms tend to progress, and when the drug is withdrawn, the condition of patients improves. Chronic drug-induced hepatitis may develop during administration of many drugs, e.g. paracetamol, isoniazid, diclofenac, methotrexate, azathioprine, etc.

Steatohepatitis. Drug-induced steatohepatitis usually develops against a background of long-term administration of drugs, especially corticosteroids, synthetic estrogens, amiodarone, calcium antagonists, antimalarials, tamoxifen. It should be considered that for the development of drug-induced steatohepatitis is not necessarily the presence of non-alcoholic fatty liver disease and its predisposing factors - diabetes mellitus, obesity of central genesis and dyslipidemia - as a background process. The histological appearance of this type of LTBI resembles that of alcoholic liver disease or non-alcoholic steatohepatitis.

To diagnose possible LBP, a careful medical history must first be taken, including medications used for self-medication (laxatives, contraceptives, analgesics, dietary supplements, etc.). Attention should be paid to the temporal relationship between drug intake and onset of symptoms, as well as the evolution of the condition after drug withdrawal .

Several factors contribute to the risk of liver damage from dietary supplements:

1. dietary supplements usually consist of multiple components, making it virtually impossible to identify the specific substance responsible for the development of a pathological reaction.
2. lack of any formal monitoring of the adverse effects of dietary supplements.
3. aggressive marketing policies of dietary supplement manufacturers.

There are currently no specific diagnostic tests for LPP, making it necessary to perform a thorough clinical and laboratory, instrumental and, if possible, morphological examination to rule out other liver diseases. The iatrogenic origin of liver damage should be taken into account for any hepatitis-like condition in middle-aged and elderly patients, especially in women. Specific diagnostic criteria systems can be used to better assess the likelihood of a drug-induced process. In particular, the international criteria for assessing LPS developed by a consensus conference (29) suggest that the following parameters should be evaluated:

1. Time interval between drug intake and development of hepatotoxic reaction:

- ✓ "presumptive" - from 5 to 90 days;
- ✓ "compatible" - 90 days.

2. the course of the reaction after withdrawal of the drug:

- ➢ "very presumptive" - decrease in liver enzyme levels by 50% of excess above the upper limit of normal within 8 days;
- ➢ "presumptive" - decrease in liver enzyme levels by 50% within 30 days for hepatocellular and 180 days for cholestatic lesions.

3) Exclude an alternative cause of the reaction by careful examination, including liver biopsy.

4. A positive response to re-injection (at least a 2-fold increase in enzyme levels) when tolerated.

A reaction is considered "drug-related" if it meets the first three criteria or two of the first three and the fourth criterion. In addition, the CIOMS/RUCAM scale can be used to determine the relationship between drug intake and the occurrence of liver damage. The scale takes into account the time interval from the start of the drug to the onset of the reaction, risk factors, the patient's progression after withdrawal, concomitant drug therapy, exclusion of causes unrelated to the drug, information on hepatotoxicity, both in the drug's instructions and in various publications, and response to re-treatment. The principle of the scale is to sum the scores on the above criteria.

This algorithm is the standard tool for determining the possible hepatotoxicity of a drug and is currently considered to be the most reliable compared to other scales for the diagnosis of LTBI : (a) hepatic abnormalities in the liver.

Abnormal liver changes usually disappear with withdrawal of the causative drug (if they do not, look for another cause). A particular challenge for the physician is the development of drug-induced HT in patients who have been prescribed the "causative" drug for a vitality-related indication. The most rational approach to prevent HT of drugs when they cannot be withdrawn is simultaneous prescribing of drugs with hepatoprotective properties.

From the point of view of evidence-based medicine, the most effective drugs for the correction of LPT, intrahepatic cholestasis include ursodeoxycholic acid (UDCA) and ademetionine, as they have a multifaceted spectrum of action, which provides therapeutic opportunities for their use [10,16].

The large number of potentially hepatotoxic drugs, as well as the diversity of the spectrum of LPS causes significant difficulties both in the diagnosis and in the treatment of these conditions. To date, there are no clear criteria for clinical, laboratory and morphological diagnosis of drug-induced liver damage, no unified classification and no treatment standards have been developed.

It is necessary to diagnose LPP at the earliest possible time, since the continued use of drugs that are suspected of causing liver damage can multiply the severity of clinical manifestations and significantly affect the outcome of the disease. Все выше изложенное обуславливает актуальность проблемы дальнейшего изучения особенностей возникновения ЛППП у пациентов ревматологического профиля, находящихся на длительной терапии метотрексатом [12]. All of the above makes the problem of further study of the peculiarities of the occurrence of LTBI in rheumatological patients on long-term therapy with methotrexate urgent [12]. In addition, the development of methods of prevention, diagnosis, monitoring of side effects during methotrexate therapy, as well as methods of treatment to reduce the toxic effects of cytostatics on the body while maintaining their sufficient effectiveness, which could be widely used in clinical practice, is promising [2,6].

Preventive measures should be implemented to minimise the risk of developing LTBI, including

- ✓ Appropriate drug administration (dose, multiplicity, routes of administration;
- ✓ not prescribing drugs with potential hepatotoxic effects in patients with risk factors;
- ✓ avoid multipragmasy, taking into account drug interactions;
- ✓ monitor liver function during pharmacotherapy if a patient has an STD risk factor and if a drug with potential hepatotoxic effects is prescribed;
- ✓ inform the patient about the potential hepatotoxic effects of the drug to be prescribed;
- ✓ inform the patient about medicines that have the same 'causative' effect
- ✓ make an early diagnosis of drug-induced liver damage;
- ✓ minimise alcohol consumption, exposure to occupational hazards;
- ✓ Treat and stabilise comorbidities (hypothyroidism, diabetes mellitus, etc)[27].

Conclusions: On the basis of all the above, numerous data on hepatotoxic effects of various drugs allow us to conclude that PDA is one of the most important problems not only for gastroenterologists, hepatologists, but also for physicians of other specialties. In developed countries, drug intake is the leading cause of liver failure and the most frequent indication for liver transplantation (26). [26].

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