Steatohepatitis is a variant of the drug-induced liver disease

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Drug-induced liver disease (DILD) is a clinical-pathological form of liver disease that develops in patients receiving medicinal products [25]. LBE true incidence is unknown, but it has been estimated that in the United States, severe liver damage drugs account for 5% of all hospital admissions, ranking from fourth to sixth place among the leading causes of death [31]. In 1970-s DILD was the cause of 2% to 5% of hospitalizations for jaundice, and in 1980 — more than 10% [33].

Steatohepatitis is a rare form of DILD, less than 2% of all cases of non-alcoholic steatohepatitis (NASH) are drug-induced [38]. Roles of one or more drugs with their cross metabolism requires evidence steatohepatitis development. It is necessary to establish a temporary connection between the disease and the onset of medication, lack of liver disease prior to taking medication, and positive clinical dynamics after discontinuation of the drug. In addition, currently there is a high prevalence of NASH in a population scale, which also creates certain difficulties to clarify the etiological factors of the disease [28]. Medical steatohepatitis has more in common with alcoholic liver disease than non-alcoholic liver disease, which is associated with obesity, diabetes and insulin resistance syndrome. The progression of fibrosis, transforming it into cirrhosis of the liver in drug steatohepatitis, is much faster (weeks or months), while liver cirrhosis in the outcome of NASH is extremely rare, and when it does occur, while the formation of cirrhosis is stretched to decades [27].

Drugs that are capable of provoking steatosis and steatohepatitis, can be divided into three main groups:

1. Drugs that directly cause steatosis and steatohepatitis. The mechanism of liver toxicity of these drugs is well understood. These include: amiodarone, perhexiline maleate, synthetic estrogens, tetracycline, methotrexate, statins.

2. Medications that can make heavier and complicate the course of NASH in predisposed individuals, increasing insulin resistance, central obesity, diabetes and hypertriglyceridemia. For example, tamoxifen, acetylsalicylic acid, sodium valproate, trimethoprim/sulfamethoxazole, calcium channel blockers (nifedipine), aminohinolony (delagil, Plaquenil), antiretroviral drugs [6, 39].

3. Medications that cause sporadic cases of steatosis/steatohepatitis without studying pathological mechanisms of liver damage, such as karbomazepin [35].

Drug-induced steatohepatitis associated with long-term treatment (more than 6 months), and possibly the drug accumulation in the body. The pathogenesis of drug steatosis/steatohepatitis resembles alcoholic liver disease. Morphological changes in the liver during the drug steatohepatitis: there is a significant inflammatory cell infiltration, inhibited the process of fatty acid.beta.-oxidation in mitochondria and disrupts the electron transfer processes in the respiratory chain, which contributes to the activation of lipid peroxidation. High blood concentration of certain drugs can directly inhibit the enzymes of the respiratory chain, resulting in the proton gradient is reduced, the level of ATP (adenosine triphosphate) and NADH depletion occurs (nicotinamide adenine **dinucleotide),** which has an additional adverse effect on the beta-oxidation of [26, 29]. Taurus Mallory are a feature of ultrastructural changes in medical steatohepatitis. They are associated with fosfolipidozom, which is dose-dependent complication, and physicochemical properties of the drug hepatotoxicity [19]. Medications causing fosfolipidoz can disrupt the synthesis of lysosomal phospholipase directly or by binding to phospholipids, thereby inhibiting the formation of lipid membrane biosloya hepatocytes [34]. While liver enzymes (transaminases and alkaline phosphatase) is commonly normalized after discontinuation of the drug-resistant liver disease and cirrhosis are retained even after discontinuation of the drug [17, 23, 36].

Another morphological variant dosage of fatty liver as an acute, subacute or chronic macrovesicular steatosis is the result of "mitochondrial injury" and occurs when taking such drugs as cocaine, tetracycline, valproic acid, zidovudine, amineptine, amiodarone, ibuprofen, pirprofen, fialuridin, panadiplon, tianeplon, atsetamifen [22, 30].

Recognition of hepatotoxicity drugs is crucial to prevent the development of severe liver disease. Early diagnosis of drug liver damage is of particular importance because of the high risk of disease progression without discontinuation. The possibility of such losses is taken into account with abnormal liver function in patients receiving different drugs as well as herbal medicine and alternative medicine drugs [2, 14]. To assess the degree of liver damage is necessary to assess the level of cytolysis and functionality of the liver, which are biochemical markers of serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum total protein and albumin, serum lipid profile.

Diagnosis LBE is placed with a history indication receiving any drug or alternative means to the exclusion of other causes and, primarily, of viral hepatitis (hepatitis A, B, C, cytomegalovirus, Epstein-Barr et al.), Autoimmune hepatitis, metabolic and cholestatic liver diseases and biliary system. Clinical, biochemical and morphological pattern LBE mostly indistinguishable from those of other etiology diseases (acute or chronic hepatitis, acute or chronic cholestatic disorders, alcoholic liver disease, etc.), its diagnosis is based mainly on the assumption of the attending physician. Held in the UK analysis of spontaneous reports of hepatotoxic reactions showed that about half of the cases a causal relationship with the drug (drug) is not [18]. In order to determine the causal relationship DILD with the drug developed several scales, among which the most widely used manufacturers and regulators gained scale RUCAM (Roussel Uclaf Causality Assessment Method), based on an assessment of the following criteria: the time of occurrence of DILD, its clinical course, factors risks associated with drugs, "non-drug" causes LBE published information about hepatotoxicity "suspect" drug and its response to the re-introduction [21]. However, targeted study to identify drug liver disease (Drug-Induced Liver Injury Network), showed that RUCAM method can't be regarded as a reliable tool for studying the DILD. Thus, to date there are no reliable methods of determining the causal relationship with the drug DILD. One of the most important criteria in determining the causal link is the resumption of unwanted reactions upon repeated administration of the drug. However, the re-appointment of drugs after the cessation of treatment is associated with a high risk, because it can lead to the rapid development of more severe recurrence LBE [12, 37].

The following parameters are taken into account to confirm the etiological role of the drug in liver disease [20]:

1. The time interval between drug administration and the development of hepatotoxicity. The etiological relationship is considered hypothetical, if the length of the interval from 5 to 90 days, and certain — 90 days or more.
2. The speed of the normalization of the disturbed functions after discontinuation of the drug. The etiological relationship is considered to be very conjectural, if elevated levels of liver enzymes is reduced by 50% for 8 days; presumably — for 30 days for hepatocellular and 180 days for cholestatic liver disease.
3. Exclusion of other causes of liver disease.
4. Development of similar hepatic lesions (at least, increased enzyme levels in the times 2) upon repeated administration of the drug, if appropriate.

The development of pathological changes in the liver is considered drug-related if the first three criteria or two of the first three and the fourth test [7]. Liver biopsy shows if there is doubt about the diagnosis of drug-induced hepatotoxicity or concerns about previously installed alleged drug hepatotoxicity. Biopsy typically not shown in the cases where the previously known hepatotoxicity proved PM [24, 32].

Treatment of DILD. In most cases, the first step in treatment is the removal of the drug, which in itself can contribute to the improvement of clinical and laboratory data. With the development of severe hepatitis require removal of the drug. Main gepatoprotektory used in the treatment of DILD: ursodeoxycholic acid, essential phospholipids (EFL), silymarin, hepatocellular components of metabolic cycles (ademetionine, ornithine aspartate, alpha-lipoic acid). In the presence of highly active hepatitis, immune-mediated reactions and glucocorticosteroids are used. When LBE flowing type steatosis/steatohepatitis, positive effect can be achieved by assigning essential phospholipids [4, 8].

Given the important role of lipid peroxidation of cell membranes in the pathogenesis of drug-induced hepatitis, hepatic seems appropriate appointment from EFL Group in various forms of DILD. Phospholipids regulate cell membrane permeability to ions is maintained oxidation and phosphorylation processes in the cell and directly to the mitochondria. Unsaturated fatty acids contribute to the activity

of phospholipids and membrane fluidity, normalize their permeability. The range of EFL activities also include: activation of RNA synthesis; normalization of protein metabolism; elevated levels of glycogen in the liver; increasing the detoxification function of the liver; conversion of neutral fat and cholesterol in the form of readily metabolized; reduction in the level of liver energy costs; reduction and disappearance of fatty infiltration of the hepatocytes; stabilization of the physico-chemical properties of bile [15]. Membrane and hepatoprotective effect is achieved by direct embedding EFL phospholipid molecules in the structure of damaged liver cells, replacement of defects and restore the barrier function of membranes. Hepatoprotective effect of the drug is based on the inhibition of lipid peroxidation, which are considered as one of the leading pathogenetic mechanisms of liver lesions.

Representatives of the group of essential phospholipids is a drug Essliver Forte (production Nabros Pharma (India), JSC "Nizhpharm" (Russia), which is a combination product that contains essential phospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidyl nozitol) [5, 10] in conjunction with vitamins B_1, B_2, B_6, B_{12}, PP and E. vitamin supplement numerous effects of phospholipids:

- Vitamin B_1 protects cell membranes from toxic effects of peroxidation products, ie It acts as an antioxidant and an immunostimulant;
- Vitamin B_2 — participants in the process of regulation of higher nervous activity;
- Vitamin B_6 is a coenzyme for amino acid decarboxylase enzymes, regulating protein metabolism;
- Vitamin B_{12} allows the formation of enzyme required for the production of lipoprotein in the myelin tissue;
- Vitamin PP (nicotinamide) is involved in the processes of tissue respiration, lipid and carbohydrate metabolism;
- Vitamin E — a powerful natural antioxidant that protects polyunsaturated fatty acids and lipids of cell membranes from peroxidation and free radical damage. It can perform a structural function by interacting with phospholipids of biological membranes.

Information about Forte Essliver incompatibility with other drugs are not available, indicating the feasibility of its use in the treatment of various diseases as a hepatoprotective. Especially important this gepatoprotektsiya patients at risk for drug steatosis/steatohepatitis.

GM Bondarenko et al. included in the complex therapy of urogenital trichomoniasis Essliver Forte gepatoprotektsii the purpose [3]. When conducting research on the biochemical blood parameters reflecting liver function in patients with urogenital trichomoniasis in the two groups being compared, it was found that taking Essliver Forte containing essential phospholipids, in parallel with the reception of imidazole and antibiotics will significantly reduce their negative effect on hepatocytes.

OA Chernov to protect TB patients from the side effects of antibiotic therapy researched gepatoprotektor Essliver fort and its effectiveness compared with other hepatoprotectors plant origin [13]. The findings of this study: the use Essliver forte in patients with pulmonary tuberculosis patients receiving massive antibiotic therapy, significantly reduced the number and severity of hepatotoxic reactions; avoid situations that require temporary cessation of chemotherapy that reduces treatment time and prevents the development of MDR M. tuberculosis; maintain regimen in one of the most effective drugs (rifampicin); to achieve the best results of TB treatment.

VA Polivanov revealed significant economic benefits of the drug before the drug Essliver Forte Essentiale Forte N with steatosis/steatohepatitis alcoholic etiology [9].

One of the studies was the experience of Essliver Forte in treatment of fatty liver and steatohepatitis, which was conducted from November 2006 to March 2007 on the basis of the Central Research Institute of Gastroenterology [16]. The study involved patients with chronic liver disease who are on inpatient or outpatient treatment. Patients participating in the study underwent a course of therapy Essliver Forte 12 weeks (3 months). Based on these results it was concluded that Essliver Forte is a drug of choice for patients with diagnoses of steatohepatitis and fatty liver.

A comparative study of the efficacy and Essliver Forte Essentiale N in patients with alcoholic liver disease in the stage of steatosis/steatohepatitis was conducted in four clinical centers (Moscow, Yekaterinburg, Kazan, Nizhny Novgorod). The study included 100 men and women aged 18 to 65 diagnosed with alcoholic liver disease. There was no statistically significant difference in the overall small clinical effect: patients in group Essliver forte — 48%, in the group of Essentiale N — 46%. In both groups was statistically and clinically significant reduction in the severity of asthenic-vegetative

syndrome, normalization of ALT, AST, albumin, GGT, globulin, total protein, prothrombin and alkaline phosphatase and improved ultrasound picture (reduced size of the liver, reducing its echogenicity and height " sound attenuation pole "in the liver). Furthermore, in the group Essliver forte statistically significant positive dynamics of glucose, total bilirubin, and indirect bilirubin fraction, a-amylase in the blood. Both groups had recovery of protein-synthetic function of the liver, and the synthesis of clotting factors. It was also noted significant improvement in quality of life assessments in both groups of patients. Assessment of viability and social activity after completion of therapy in a group Essliver fort were significantly higher than in the group Escentsiale N. Thus, doubtless quite high clinical efficacy Essliver Fort [11].

Clinical studies conducted with Essliver Forte in Russia, once again proving the high efficiency of essential phospholipids in combination with vitamins in the treatment of various liver diseases, which are used in hepatology for over 50 years and also have a great number of positive clinical observations. Experience in the use of combined hepatoprotective drug Essliver Forte in clinical practice in patients with chronic metabolic diseases of the liver showed that the drug helps slow down the transformation of any etiology of hepatitis to cirrhosis of the liver, normalize lipid and carbohydrate profile. Due to the complex impact on the various links in the pathogenesis can reduce the number of drugs taken at the same time, it contributes to the treatment of compliance and quality of life [1].

Thus, Essliver Forte has a distinct safety profile. It is well tolerated by patients and even chronic administration rarely causes side effects. This is due primarily similarity essential phospholipids and phospholipid organism. Secure with a long reception, good tolerability and efficacy of essential phospholipids allow attributed to first-line drugs for the prevention and treatment of various forms of drug-induced steatosis/steatohepatitis.

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This work is devoted to drug liver lesions that develop of the type of steatosis/steatohepatitis. This disease is not frequent, but if it has been developing on the background of hepatic steatosis (alcoholic or non-alcoholic), its course can be quite serious. The classification of drugs causing a variety of options of fatty liver is presented. We describe the pathogenic mechanisms of drug-induced liver lesions of the type of steatosis/steatohepatitis. Chapter considering the treatment of drug-induced steatosis/steatohepatitis provides current data on the use of essential phospholipids as the drugs of choice upon the described pathology. The drug Essliver Forte is one of the effective means appointed for both prevention and treatment of drug-induced steatosis/steatohepatitis.