Drug-induced liver lesions: modern approaches to treatment

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The slogan of clinical pharmacology should be "Less medicines — only the most necessary", and not "What else to give the patient?"... It is necessary to treat when it is impossible not to treat.

B. E. Votchal [7]

Drug-induced liver lesions (DILL) are morphological and functional changes in the hepatic tissue caused by medication intake or by their incorrect dosage [10].

Acute drug damage to the liver can be provoked by a large number of drugs (about 1 thousand), about 200 of which are potentially hepatotoxic [11].

Chronic drug damage to the liver develops much less frequently. In general, drugs account for almost 40% of all cases of hepatitis and 25% of cases of fulminant liver failure. Medical lesions of the liver occur in general medical practice with a frequency of 0.3 cases per 100 thousand patients, although the data of a number of pharmacoepidemiological studies suggest that these figures are understated [12].

Annually more than 1 million people suffer from side effects of pharmacotherapy and about 180 thousand patients die from them [3, 9].

DILL is one of the main causes of liver transplantation in Europe and the United States and 7.4% of the causes of all deaths from adverse reactions [2].

The main principles of treatment are shown in Table 1.

Table 1

The main principles of treatment of drug-induced liver lesions
(according to V. T. Ivashkin et al., 2016 [1])

Basic principles of therapy	Comments
Abolition of the drug that caused liver damage	As a rule, leads to the disappearance of clinical symptoms, the normalization of biochemical blood parameters and the restoration of the morphological structure of the liver
Application of antidotes	Perhaps only in some cases: for example, the antidote of paracetamol is N-acetylcysteine, and when poisoning with pale toadstool, silymarin or penicillin
Purpose of glucocorticosteroids	Reasonable in hypersensitivity reactions
Prevention of glutathione depletion	Ademethionine
Effects on cytochrome P450, mitochondrial dysfunction, cytokines (TNF- α)	UDCA, silymarin, glycyrrhizic acid
Liver transplantation	In severe cases with progressive hepatic failure

Fundamentally important is the withdrawal of the drug that caused DILL. Exceptions are possible under the following conditions:

- the drug is vital and there is no way to replace it;

- increased transaminases ≤ 3 norms;
- with dynamic observation there is no further increase in transaminases ;
- absence of clinical manifestations;
- absence of pregnancy (with pregnancy cancellation is mandatory).

The use of antidotes is rarely possible (Table 1).

Diet includes recommendations for healthy nutrition with moderate protein content of at least 60–100 g/d. Only when liver failure is considered the problem of protein restriction.

Glucocorticoids are shown to all patients with immuno-mediated DILL, as well as for moderate to severe and severe male with any pathogenesis. Consider the presence of diabetes mellitus, concomitant infection, gastrointestinal bleeding. In the presence of these conditions in each specific case, it is necessary to carefully analyze the relationship between the use and risk of the appointment of glucocorticosteroids. In the absence of contraindications, corticosteroids are administered first parenterally for several days, then an oral intake is prescribed.

Pathogenetically justified is also the appointment of hepatoprotectors (ursodeoxycholic acid (UDCA), silymarin, ademethionine, L-ornithine- L-aspartate, essential phospholipids), infusion therapy, thiopoietins, pentoxifylline, vitamins [5].

Application of ademethionine it is pathogenetically justified as a means to increase the synthesis and stores of glutathione in the liver, it is indicated in the case of the DILL associated with the action of toxic metabolites of the drug, with glutathione deficiency and the need to continue receiving the drug that caused the DILL. Evidence based studies confirming the efficacy of ademetionine in BOP are not conducted. The expediency of prescribing this drug in DILL, accompanied by cytolysis and cholestasis, is determined by the experience of individual clinics and specialists. The oral form of ademetionine has a low bioavailability, so the decision to assign the drug should only assume its parenteral administration at a dose ≥ 800 mg/day in order to achieve the saturating concentration in the tissues, followed by oral reception at a dose 1600 mg/day. In our opinion, the sublingual form of ademetionine is promising, but its effectiveness and safety, incl. While DILL requires further research.

Silymarin/silibinin has an evidence base for treatment of DILL, but randomized clinical trials in this area were conducted exclusively with Legalon. Original silybinin (Legalon) is highly effective in fatty liver dystrophy of nonalcoholic etiology, induced by exposure to hepatotoxic drugs. It was found that the activity of glutamate-pyruvatetransaminase in patients with fatty liver dystrophy or drug-induced hepatitis receiving silibinin was normalized for 7 days, whereas in patients taking placebo, such a result was achieved only on day 23. Glutamate oxalate transaminase normalized, respectively, on the 10th and 14th days [8]. Significant effectiveness of the original silybinin (Legalon) for medicinal hepatitis, including those associated with the use of psychotropic drugs, is shown in an open controlled study [21], as well as in a double-blind placebo-controlled study with parallel groups [15].

The administration of L-ornithine-L-aspartate is indicated for liver failure, encephalopathy [17].

Essential phospholipids do not have sufficient evidence base for DILL (expert opinion). Presumptive mechanism of their action is based on the stabilization of membranes and indirect effect on the activity of cytolytic syndrome. In the countries of the former USSR, essential phospholipids are used frequently, although in the European Union and the United States they are not used in clinical practice, since randomized placebo-controlled clinical trials, in particular Veterans Affairs Cooperative A study conducted in 2003 that included 789 patients with alcoholic and mixed (alcohol-viral) etiology of hepatitis did not reveal any positive effects of these drugs on liver function compared with placebo [22]. Moreover, it was found that in acute and chronic viral hepatitis, they are contraindicated, since they can contribute to strengthening the cholestatic syndrome and increase cytolysis [6]. In our opinion, preparations of essential phospholipids can be administered with steatosis of the liver, inactive steatohepatitis, which developed as a result of toxic damage to the liver.

A universal hepatoprotector with DILL, which is shown in any pathogenetic variant of the development of the examined state, is UDCA (Table 2).

Table 2

Differentiated therapy of DILL, depending on the prevailing mechanism of development (according to E. Y. Eremina, 2012 [5])

Prevailing mechanism	Glucocorticoo steroids	UDCA	Silibinin	Ademethionine	Phospholipids	Pentoxifylline
Direct cytolytic	+	+	±	-	±	+
Direct cholestatic	-	+	-	±	-	-
Direct mixed	±	+	±	±	±	±
Toxic effect of metabolites of drugs	-	+	±	+	+	-
Idiosyncrasy	+	+	±	-	-	±
Immunoallergic DILL	+	+	-	-	-	+

Dedicated more than a hundred years ago, UDCA has been used in practical medicine since the mid-1970s after describing its ability to desaturate bile and dissolve cholesterol stones. With the accumulation of clinical experience, other positive effects of UDCA on intrahepatic bile circulation, hepatocyte metabolism, and mucous membrane of the upper half of the digestive tract have been proven, which significantly increased the indications for its use.

At present, UDCA is used for cholelithiasis (CHD), cholestatic liver diseases, viral, alcoholic, medicinal hepatitis, non-alcoholic steatohepatitis, cholesterosis of the gallbladder, reflux gastritis and other conditions.

In the liver of cholesterol, primary bile acids are synthesized — cholic acid and chenodeoxycholic acid (HCDA). Of these, deoxycholic and lithocholic acids (secondary bile acids) are formed in the intestine as a result of deconjugation and dehydroxylation reactions under the influence of the intestinal flora. UDCA is a tertiary hydrophilic bile acid, which is formed from HCDA. UDCA is no more than 5% of the total pool of bile acids contained in bile. The hydrophobic properties of bile acids and the associated toxicity increase in the following order: cholic acid → UDCA → chenodeoxycholic acid → deoxycholic acid → lithocholic acid. This relationship of hydrophobicity and toxicity of bile acids is due to the fact that hydrophobic acids are lipophilic, this property allows them to penetrate lipid layers, including cell membranes and mitochondrial membranes, provoking disruption of their function and death [4]. The higher polarity of UDCA correlates with the lower tendency to micelle formation, which explains the absence of toxicity of this acid. When administered at a dose of 13-15 mg/kg/day, UDCA replaces toxic bile acids and accounts for about half of the bile acid pool in bile.

Mechanisms of action of UDCA (according to I. N. Grigorieva, 2012 [4])
Litholytic effect: - decrease in bile lithogenicity due to formation of liquid crystals with cholesterol molecules, prevention of formation and dissolution of cholesterol stones.
Anticholestatic effect: - inhibition of the secretion of toxic bile acids into bile due to competitive uptake by receptors in the ileum; - stimulation of exocytosis in hepatocytes by activation of Ca^{2+}-dependent α-protein kinase, which causes a decrease in the concentration of hydrophobic bile acids.
Choleretic effect: - induction of bicarbonate choleresis, enhancing the excretion of hydrophobic bile acids into the intestine; - the displacement of the pool of toxic hydrophobic bile acids due to competitive capture by

receptors in the ileum; - stimulation of exocytosis in hepatocytes by activation of calcium-dependent α- protein kinase (leads to a decrease in the concentration of hydrophobic bile acids).
Cytoprotective effect: - incorporation of UDCA into the phospholipid layer of the cell membrane with its stabilization and increase in resistance to damaging factors.
The differential effect on the regeneration of hepatocytes: - stimulation of mitosis and hepatocyte regeneration after liver resection in experimental animals; - inhibition of proliferation of hepatoma cells in humans.
Modulation of apoptosis: - decrease in Ca^{2+} concentration in cells, preventing the release of cytochrome C from mitochondria, which in turn blocks the activation of caspases and apoptosis cholangiocytes ; - inhibition of apoptosis hepatocytes in cholestatic liver diseases; - The antiapoptotic effect of UDCA is not limited to the liver alone, but also occurs in the central nervous system (CNS); - in the mucosa of the colon, UDCA influences apoptosis in the opposite way — it stimulates it.
Immunomodulating effect: - reduction in the expression of HLA class 1 molecules on hepatocytes and HLA class 2 on cholangiocytes, which reduces their autoimmunity ; decrease in production of proinflammatory cytokines (interleukins 1, 6, γ -terferon).
Anti-inflammatory effect: - a decrease in the initially elevated eosinophil level and prostaglandin E_2 content in the blood in patients with primary biliary cirrhosis; - a decrease in the activity of phospholipase A_2 in the blood of patients with chronic liver disease; - inhibition of the release of inflammatory mediators from mast cells in inflammatory bowel diseases.
Antitoxic effect against CNS and liver: - inhibition of induced hyperbilirubinemia apoptosis astrocytes (in animal experiments); - mobilization of transport systems of central nervous system neurons responsible for elimination of toxic bile acids from it; - neuroprotective action; - induction of CYP3A4 in the liver.
Hypocholesterolemic effect: - decrease in absorption of cholesterol in the intestine, synthesis of cholesterol in the liver and excretion of cholesterol in bile.
Antitumor effect: - prevention of colon cancer-specific cellular (Ras) mutations; - blocking the activation of "wild" types of Ras ; - suppression of expression on cancer cells of cyclooxygenase-2; - stimulation of apoptosis in the colonic mucosa.

Of particular importance in the treatment of DILL is not only antitoxic, but also *antioxidant effect of* UDCA. Numerous experimental studies have established that UDCA is capable of binding the superoxide anion and hydroxyl radical, the most active forms of hydroxyl radicals, i.e. is an antioxidant of direct action. UDCA also contributes to an increase in the concentration in glutathione cells, which is a component of the intracellular antioxidant system. In addition, UDCA suppresses mitochondrial activity oxidase enzymes responsible for

production of superoxide anion. Thus, UDCA inhibits lipid peroxidation and reduces oxidative stress, i.e. restores the balance of oxidants and antioxidants in the cytoplasm of hepatocytes [10].

At chronic DILL the *antifibrotic effect of* UDCA is important. It is dose-dependent and is caused by a decrease in the number of receptors to the transforming growth factor−1 (TGF-β1), due to a decrease in their synthesis. Against the background of receiving UDCA, a decrease in the content of the matrix RNA, which determines the synthesis of this receptor in stellate cells, is registered. As is known, TGF-β1 is released by damaged hepatocytes and is the main activator of stellate cells — the key cells in the process of fibrogenesis. Their activation is achieved by binding of TGF-β1 receptors located on the surface of stellate cells. In addition, under the influence of UDCA, synthesis intensifies and the concentration in the cytoplasm of intracellular kinases, inhibitors of cell activation, increases. All this leads to a significant slowdown in the process of fibrogenesis in the liver [10].

Various mechanisms of action of UDCA allow to use it for all forms of male lesions, especially those with cholestasis.

The effectiveness of UDCA in the case of male breast cancer has been demonstrated in a number of case studies. Use of the drug in patients with diabetes mellitus receiving flucloxacillin over infected diabetic foot ulcers, contributed to the normalization of serum bilirubin levels 16 — 21 days [19]. P provided UDCA efficiency in cholestasis associated with taking amiodarone [13]. With the help of UDCA it is possible to achieve the resolution of cholestasis caused by phenothiazine/prochlorperazine [14], immunosuppressants prescribed after heart transplantation [16], anabolic steroids [18].

UDCA can be used for the prevention of DILL in the appointment of hepatotoxic drugs, in particular, methotrexate. It has been shown that U DHC prevents necrosis of hepatocytes and inflammation [20].

For detoxification performed infusion of 5% glucose solution, Ringer's solution, Ringer's lactate, starch hydrolysates, succinic acid, L-ornithine-L-aspartate 5-10% albumin (has a high binding capacity), etc. In severe cases plasmapheresis is prescribed.

W hen assessing the prognosis for life using a rule «Hy's Law: a combination of severe hepatocellular lesions (ALT > 3 norms) and jaundice (bilirubin > 3 norms) is associated with a poor prognosis — lethality > 10% [1].

Acute liver failure in male patients is more likely to develop in women. When fulminant hepatic failure due DILL mortality reaches 30 — 50%.

In the general population persons taking drugs, mortality or the need for liver transplantation with an increase of bilirubin level and ALT ≥ 2N assuming no obstruction is 2.4-14.3%, depending on the drug [5].

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The article presents a modern definition of drug-induced liver lesion, epidemiology of such lesions. The main attention is paid to a treatment. The therapeutic capacities of various hepatoprotectors have been compared, the advantages, mechanisms of action of ursodeoxycholic acid have been highlighted. The literature data on the prognosis of the drug-induced liver lesions are also presented.