MEDICATIONS LIVER DAMAGE

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Annotation: *The article presents literature data on the problem of drug-induced liver damage. A case of chronic drug-induced hepatitis is described.*

Key words*: drug-induced liver damage, drug effect on hepatocytes, drug-induced hepatopathy, drug-induced hepatitis.*

Drug-induced liver damage is one of the pressing problems of modern medicine. According to the Committee on the Safety of Medicines, in the UK and France they account for about 10-15% of all adverse reactions of the body to taking pharmacological drugs. In the United States, one in four cases of fulminant liver failure is due to medications. Drug-induced hepatopathies are the cause of acutely developed jaundice in 2.5-3% of cases in the USA and 3-4% in Europe [1,3,4,6,7]. In patients over 40 years of age, this figure can reach 40% [5]. In a recently completed domestic study, analyzing data from 2300 patients with various liver dysfunctions, acute drug-induced hepatitis was diagnosed in 62 (2.7%) [4]. The given indicators do not fully reflect the state of the problem. There are a number of subjective and objective factors that make it difficult to collect data on the frequency of drug-induced liver injuries. These include [2]: their frequent latent course, polypharmacy, self-medication with dietary supplements and “folk remedies”, patient secrecy, insufficiently carefully collected anamnesis, inadequate interpretation of clinical and instrumental data, the desire by medical workers to hide side effects in order to avoid professional, civil or criminal responsibility.

There are three main mechanisms of toxic effects of drugs on the liver: the direct effect of the drug on hepatocytes, the direct effect of drug metabolites on hepatocytes, and the immunoallergic effect. The first, due to the tightening requirements of the pharmacovigilance system, is currently rare. The leading mechanisms are the direct influence of toxic metabolites formed during the biotransformation process on liver cells and the formation of metabolites, which are haptens for liver cell proteins and cause immune damage.

The liver's response to a drug depends on factors related to both the properties of the drug itself (its physicochemical characteristics, dosage form, dose, routes of administration, number of drugs taken simultaneously) and the characteristics of the patient (hereditary predisposition, individual sensitivity, initial condition of the liver, gender, age, concomitant pathology, pregnancy, alcohol intake, environmental characteristics) [3].

Almost all drugs have the potential to cause liver damage. Their hepatotoxic effects are divided into dose-dependent (manifested when taking a larger amount of the drug) and dose-independent (due to idiosyncrasy). The first are typical for: antidepressants, tranquilizers, sedatives, hormonal drugs, cytostatics, antibiotics, etc.

The second ones are for NSAIDs, diuretics, antidiabetic, thyriostatic, antiparasitic drugs, etc.

A modern classification of drug-induced hepatopathy in everyday life was proposed by S. Sherlock, J. Dooley (2000). It is based on pathomorphological changes in the liver: necrosis of hepatocytes of the I and III zones of the acinus, mitochondrial cytopathy, steatohepatitis, acute and chronic hepatitis, fibrosis, allergic reactions, cholestasis (tubular, parenchymal-tubular, ductular), vascular reactions (veno-occlusive disease, dilation of sinusoids and peliosis, obstruction of the hepatic and portal veins), biliary reactions (sclerosing cholangitis, thickening and stagnation of bile in the gallbladder), neoplastic reactions (focal nodular hyperplasia, adenohepatocellular carcinoma). They are distinguished by the following clinical forms [3]: isolated increase in transaminase levels, acute and chronic drug-induced hepatitis, fulminant forms of hepatitis, liver cirrhosis. In some cases, pseudosurgical symptoms may develop (biliary colic, obstructive jaundice, acute cholecystitis, fever).

Diagnosis of drug-induced liver damage is very difficult. The doctor is required not only to carefully collect anamnesis, to carefully examine the patient physically and using modern laboratory and instrumental methods, but also to have a good knowledge of the manifestations of all known nosological forms accompanied by liver damage. The following diagnostic criteria are most often used [8]:

- chronological (cause-and-effect) relationship between the appearance of symptoms of liver damage and taking the drug (from several hours to several months);
- regression of clinical and laboratory symptoms after its discontinuation;
- relapse of pathological manifestations after repeated (usually accidental) administration of the drug;
- thorough assessment of the results of laboratory and instrumental examination of the patient;
- no other possible cause.

Establishing a diagnosis of drug-induced liver damage requires stopping the medication that caused it and, as completely as possible, canceling all medications prescribed to the patient. In this case, only vital items can be left. To date, there are no data from studies conducted from the standpoint of evidence-based medicine that would allow the development of algorithms for the treatment of certain forms of drug-induced hepatopathy. However, based on the results of experimental work and individual clinical observations, it is possible to identify certain groups of drugs that limit the degree of liver damage [3-7].

To improve metabolic processes in the liver, stabilize hepatocyte membranes and resolve cholestasis, the following is used:

- 8-adenosylmethionine at a dose of 400-800 mg per day in the first 10-14 days IM or IV, then switch to taking the drug orally, 1-2 tablets. 2 times a day;

- ursadeoxyzolic acid (UDCA) preparations at a dose of 14 mg/kg/day.

The average duration of treatment until clinical and laboratory parameters normalize is 2 months.

In the presence of clinical manifestations of hepatic encephalopathy, L-ornithine-L-aspartate is used. When administered intravenously, the dose is 20-40 g per day (40 g per 500 ml of saline). Duration of parenteral administration is 1-2 weeks. The average dose when taking the drug orally is 9-18 g/day. (up to 3-6 months).

In case of drug-induced liver damage occurring as steatohepatitis, a positive effect can be achieved by prescribing essential phospholipids (EPL) preparations, which help normalize the permeability and integrity of hepatocyte membranes. EPL is prescribed at a dose of 50 mg every 6 hours IV. A number of antioxidant drugs (alpha-tocopherol, ascorbic acid) have a certain therapeutic potential. There are individual studies demonstrating positive results when prescribing herbal products with membrane-stabilizing properties and the ability to regulate the composition and rheological properties of bile (milk thistle, artichoke, solyanka, aureus).

Preventive use of ademetionine, UDCA and EPL drugs is possible if it is necessary to prescribe drugs with a high incidence of hepatopathy.

A clinical study illustrates the chronic form of drug-induced hepatitis, which clinically manifested itself after the use of paracetamol in the treatment of ARVI. The combination of hormone replacement therapy with estrogens, which causes reversible tubular cholestasis, the use of paracetamol, leading to dose-dependent necrosis of the third zone of the acinus, against the background of treatment and ACE, beta-blockers and herbal preparations, which can also damage hepatocytes, caused the development of hepatopathy with cytolytic and cholestatic syndromes. Antibacterial therapy with cephalosporins, which intensified the formation of biliary sludge, made a certain contribution to the intensification of the manifestations of the latter. Polypharmacy is known to increase the incidence of drug-induced liver injury. So, according to V.G. Radchenko et al (2005), when taking 5 drugs simultaneously, the probability of developing side effects is 4%, 5-10 - 10%, etc. In addition to individual sensitivity and polypharmacy, other predisposing factors for hepatopathy in the given example were: female gender and episodic alcohol intake (retrospectively established by questioning the patient during the period of re-hospitalization). The exclusion of other possible causes of jaundice and hepatomegaly, complicated by the syndromes of hepatic cell failure and portal hypertension, and their disappearance with the complete abolition of drugs allowed us to establish the drug origin of liver damage.

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