Pro Index | Journal of Science in Medicine and Life
Volume: 3 Issue: 3 Year: 2025
ISSN: 2992-9202 | http://journals.proindex.uz

Drug-Induced Liver Injury in Children

Matniyozova Zaynabjon Toxtaboyevna
Bukhara state medical institute after named Abu Ali ibn Sino
matniyozova.zaynabjon@bsmi.uz

Abstract: The most common and dangerous side effect of drug therapy is hepatotoxicity. The liver, as the primary organ where drugs are metabolized, is particularly susceptible to the damaging effects of medications and toxins. Drug-induced liver injury (DILI) is the most frequent reason for the discontinuation of new drug development. In developed countries, medication use is the leading cause of liver failure and the most common indication for liver transplantation.

Key points: drug-induced liver injury (DILI), hepatotoxicity, pediatrics, hepatic metabolism, liver toxicity, adverse drug reactions (ADR), cytolysis syndrome, cholestasis syndrome, hepatic failure, biotransformation.

Currently, the most crucial condition for the use of drugs in children is the absence of significant (serious) adverse reactions, as proven by large-scale clinical trials. Extensive studies on the efficacy and safety of drugs are conducted even after their registration. Regulatory agencies may impose restrictions on their use, add additional warnings to instructions, and even withdraw them from the pharmaceutical market.

For example, in the 1970s, convincing evidence emerged that the use of acetylsalicylic acid (aspirin) in viral infections in children could be associated with Reye's syndrome, leading to toxic encephalopathy and fatty degeneration of internal organs, primarily the liver and brain. Restrictions imposed in the U.S. on the use of acetylsalicylic acid in children significantly reduced the incidence of Reye's syndrome, from 555 cases in 1980 to 96 cases in 1987 and just 2 cases in 1997. By order of the Russian Federation's Pharmacological Committee on March 25, 1999, the use of acetylsalicylic acid in acute viral infections (ARVI, influenza, chickenpox) was permitted only from the age of 15. However, under strict medical supervision, acetylsalicylic acid can be used in children with rheumatic diseases.

In March 2005, a decision was made to ban the use of nimesulide (Nise, Nimulid) as an antipyretic in children due to its hepatotoxicity (4:1000 children of all ages). Cases of fatal toxic hepatitis in children caused by this drug have been reported. Nimesulide has been banned for use in children in the vast majority of countries worldwide.

The true incidence of drug-induced liver injury (DILI) is unknown. According to global statistics, drug-induced liver damage accounts for 0.7% to 20% of acute and chronic liver diseases. In children, DILI occurs less frequently than in adults. In recent years, there has been a clear trend toward an increase in DILI cases, which is associated with the growing number of manufactured drugs, the simultaneous use of multiple medications, and the consumption of "natural" herbal and other substances, including various biologically active dietary supplements, many of which have toxic effects on the liver. For example, in Japan, the incidence of drug-induced hepatotoxicity increased 11-fold over a 30-year period.

The pharmacokinetics of drugs consists of four stages: binding of the drug to plasma proteins, transport through the bloodstream to the liver, uptake by hepatocytes (hepatic clearance), and

excretion of metabolites through urine or bile. The liver is the only organ capable of eliminating all lipophilic substances, including drugs, by transforming them into water-soluble compounds. Liver damage—ranging from subclinical forms to fatal liver failure—has been described for nearly 1,000 medications. The group of hepatotoxic drugs, including those used in pediatrics, includes antimicrobial and antifungal agents, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, anesthetics, and psychotropic medications.

The metabolism of drugs in the liver is conventionally divided into three phases. In the first phase, when a drug enters a hepatocyte, it undergoes hydroxylation or oxidation with the involvement of monooxygenases, cytochrome C reductase, and the cytochrome P450 enzyme system. This process produces toxic metabolites that can inactivate liver enzymes, damage mitochondria, reduce transmembrane electrical potential, and lead to cell death through necrosis or apoptosis. Examples of drugs that metabolize into substances harmful to liver cells include paracetamol, isoniazid, mercaptopurine, methotrexate, tetracycline, and others.

The second phase involves the biotransformation of metabolites to reduce their toxicity by conjugation with various endogenous molecules. Enzymes such as glucuronyltransferases, sulfatases, glutathione S-transferases, and acetylaminotransferases participate in these reactions, forming water-soluble compounds.

The third phase is the excretion of these substances from the liver cells.

Factors influencing the development of drug-induced liver injury (DILI) can be genetically determined or related to environmental influences. The dosage, duration of administration, and serum drug concentration (e.g., paracetamol and methotrexate) play a significant role. Genetic variability in cytochrome P450 enzyme systems and acquired polymorphism of hepatocyte conjugation systems due to environmental factors underlie individual susceptibility. This explains why the same drug can cause different DILI manifestations in different patients. For example, cholestatic reactions to amoxicillin with clavulanic acid are associated with specific HLA system classes.

Risk factors for DILI include age (children under 3 years old), polypharmacy (simultaneous use of three or more drugs), nutritional status (obesity or weight loss), pre-existing acute or chronic liver disease, and other medical conditions such as rheumatoid arthritis, diabetes, chronic kidney disease, and HIV infection.

From a pathogenetic perspective, DILI is classified into two groups:

1) Toxic reactions – caused by the direct damaging effect of drug metabolites, dose-dependent, predictable, and occurring within days of starting therapy (Type A adverse drug reactions).

2) Idiosyncratic reactions – subdivided into metabolic and immunoallergic types, which develop unpredictably over varying timeframes (from weeks to over a year) even at standard therapeutic doses (Type B adverse drug reactions).

Type B reactions are not dose-dependent and result from individual drug intolerance (idiosyncrasy). These occur due to genetically determined enzyme structural features (metabolic type) or hypersensitivity mechanisms (immunologic type). Type B reactions are difficult to reproduce in experimental settings and are typically detected during widespread drug use.

Drug-induced liver injury mediated by immune mechanisms often presents clinically with fever, rash, eosinophilia, and the formation of antinuclear antibodies. In the vast majority of cases, drug-induced liver diseases develop via an idiosyncratic mechanism.

In drug-induced liver injury (DILI), not only hepatocytes but also other liver cells (cholangiocytes, Ito stellate cells, and endothelial cells) may be affected. This explains the wide variety of clinical and morphological manifestations, including necrosis, fatty degeneration, liver cell dysfunction without structural abnormalities, cholestasis, and progressive fibrosis leading to cirrhosis. Based on

the clinical presentation, DILI is classified into three main types: hepatocellular, cholestatic, and mixed. While liver pathology can be diverse, the majority of cases manifest as hepatitis.

The hepatocellular type is diagnosed when alanine aminotransferase (ALT) activity increases more than twice the upper limit of normal (ULN), with an ALT/alkaline phosphatase (ALP) ratio >5. The cholestatic type is identified when ALP activity increases more than twice the ULN, with an ALT/ALP ratio <2. The mixed type is characterized by elevations in both ALT and ALP, with an ALT/ALP ratio between 2 and 5.

In the hepatocellular type, acute liver failure is more likely to develop. Severe jaundice with high bilirubin levels (total bilirubin >2.5 mg/dL) is associated with a poor prognosis, following Hy's rule, where approximately 10-12% of these patients die or require liver transplantation. In cases of submassive or massive necrosis, mortality can reach 86%.

The cholestatic and mixed types of liver injury are more common in patients with comorbidities, with a lower mortality rate of 5-7%.

DILI can also occur in asymptomatic forms, presenting only as biochemical abnormalities, such as increased markers of hepatocyte cytolysis, intrahepatic cholestasis, and impaired liver detoxification and synthetic functions (elevated ALT, ALP, bilirubin, and decreased prothrombin index).

The first step in diagnosing drug-induced liver injury (DILI) is a thorough review of the patient's medication history, including dosage and duration of use, while ruling out other potential causes, primarily viral hepatitis (hepatitis A, B, C, CMV, Epstein-Barr virus, etc.), metabolic diseases, and cholestatic liver and biliary system disorders.

To confirm the role of a drug in liver injury, the following criteria are recommended: Time interval between drug administration and the onset of hepatotoxicity. Rate of liver function recovery after discontinuing the drug (a 50% reduction in elevated liver enzyme levels within 8 days is indicative). Exclusion of other potential causes of liver damage. Rechallenge test: A similar liver injury (at least a twofold increase in enzyme levels) upon re-exposure to the drug.

DILI symptoms are often nonspecific and range from mild or asymptomatic cases (e.g., nausea, loss of appetite, mild abdominal discomfort with minimal lab abnormalities) to severe hepatocellular and cholestatic syndromes, including jaundice and acute liver failure. Some patients may develop systemic immune-mediated hypersensitivity reactions, presenting with fever, rash, lymphadenopathy, and eosinophilia, along with liver involvement. The biochemical evaluation of liver function is crucial for diagnosing the type of liver injury, distinguishing between cytolytic, cholestatic, immune-inflammatory, and hepatocellular failure syndromes. Cytolysis markers (hepatocyte damage severity): Elevated ALT and AST levels. Mild injury: ALT and AST levels up to 2× ULN with normal bilirubin. Severe injury: ALT and AST levels > 5× ULN, with increased total bilirubin. Cholestasis markers: Elevated GGT (gamma-glutamyl transferase) and ALP (alkaline phosphatase). In some cases, total bilirubin is elevated, with a predominance of conjugated bilirubin. Immune-inflammatory syndrome markers: ALT and AST elevation combined with: Increased gamma-globulins (≥1.5× ULN). Elevated circulating immune complexes (CICs) and immunoglobulins. Hepatocellular failure markers: Reduced prothrombin index (PTI). Often low albumin levels, indicating impaired liver synthetic function.

References:

1. Белоусов Ю.Б. Лекарственные поражения печени, ассоциируемые с макролидами. Очевидна ли связь? // РМЖ; 2011; 18: 1118-121.
2. Болезни печени и желчевыводящих путей: Руководство для врачей / под ред. В.Т. Ивашкина // М.: М-Вести, 2023. — С. 122-131.
3. Буеверов А.О. Лекарственные поражения печени // РМЖ, гастроэнтерология. — 2021. — № 9. — С. 13-14.

4. Жолобова Е.С., Конопелько О.Ю., Гешева З.В. Гепатотоксичность нестероидных противовоспалительных препаратов // Педиатрия, 2019; 5: 155-60.
5. Запруднов А.М. Синдром Рея в детском возрасте. Парацетамол в педиатрической практике. — М.: Стерлинг хелс, 2015. — С. 59.
6. Ковтун А.В., Яковенко А.В., Иванов А.Н. и др. Лекарственноиндуцированные поражения печени. Диагностика и лечение // Гастроэнтерология, 2011; 2: 35-41.
7. Муравьев Ю.В., Осипова Е.В. и др. Токсическое повреждение печени диклофенаком натрия // Клин. фармакология и терапия, 2022; 2: 94-96.
8. Радченко В.Г. Лекарственные поражения печени // Новые СПб врачеб. новости, 2024; 4: 25-29.