

## Case Report

# Acute hepatitis in a paediatric patient: immune-mediated drug-induced liver injury or albendazole-induced autoimmune hepatitis?

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## Abstract

**Introduction:** Drug-induced liver injury (DILI) is one of the most common causes of liver damage. A large number of drugs, dietary supplements, and herbal medications can cause hepatotoxicity. In some situations, it is difficult to distinguish between DILI and autoimmune hepatitis, especially when the mechanism is immune-mediated. Albendazole is a drug that has been used for decades for the treatment of parasitic infections in humans. One of the side effects is liver enzyme elevation, but rarely requires the discontinuation of therapy. Previous experience has shown that hypersensitivity is the most common mechanism of albendazole hepatotoxicity.

**Case report:** Here we presented a paediatric patient in whom albendazole induced severe liver injury. In laboratory analyses, in addition to markedly elevated transaminases and parameters of cholestasis, there was also a significant increase in IgG, so autoimmune hepatitis was considered. Even though the liver histology indicated toxic liver disease, prednisolone was started. Corticosteroid therapy resulted in the complete normalization of liver function, as well as IgG. With the cessation of corticosteroid therapy, transaminases, bilirubin and gamma-glutamyl transferase (GGT) remained within normal levels, but an increase in anti-smooth muscle antibodies (SMA) was noted in immunological analyses after one year of follow-up.

**Conclusions:** Immune-mediated hepatotoxicity from albendazole is one possible mechanism of liver injury. The use of albendazole in the treatment of parasitic infections, especially in children, requires close monitoring. The question remains as to whether albendazole is a drug that can induce autoimmune hepatitis in the paediatric population.

**Key words:** Albendazole; hepatotoxicity; cholestasis; immune-mediated; autoimmune hepatitis.

*J Infect Dev Ctries* 2022; 16(10):1660-1663. doi:10.3855/jidc.16594

(Received 19 March 2022 – Accepted 10 May 2022)

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## Introduction

One of the most common causes of acute liver damage is drug-induced liver injury (DILI). DILI is a global problem of unknown incidence. So far, over 900 medical preparations (drugs, dietary supplements, and herbal medications) that can lead to liver damage have been described, and this list is expected to grow [1,3].

Hepatotoxicity can manifest itself in the entire spectrum, from asymptomatic transaminase elevations to fulminant hepatic failure requiring liver transplantation, while chronic liver disease is extremely rare. Liver injury occurs due to dose-dependent reactions, dose-independent reactions (idiosyncratic

hepatotoxicity), or unwanted reactivation of liver disease [3].

Albendazole is a broad-spectrum anthelmintic. Along with mebendazole and thiabendazole, it belongs to the pharmacological group of benzimidazoles. Benzimidazoles act by selective binding to  $\beta$ -tubulin of the parasite, causing its immobilization and death. The use of albendazole in the treatment of helminth infections in humans has been permitted since 1996. The dose and duration of treatment depend on the indication. Generally, it is well tolerated. The most common side effects are nausea, gastrointestinal discomfort, diarrhea, transient alopecia, skin rash, and dizziness. Prolonged high doses may have hepatotoxic

and myelosuppressive effects. It is contraindicated in pregnant women [6]. According to data a slight increase in transaminases has been described in about 15.6% of patients, but only a few patients required discontinuation of the therapy. The most commonly described mechanism of hepatotoxicity is hypersensitivity [7,8]. Here we present a patient in whom albendazole induced immune-mediated toxic hepatitis.

### Case presentation

*Enterobius vermicularis* was isolated in an 8-year-old girl's stool sample while investigating chronic urticaria. Albendazole was prescribed at the regional health center as the first drug of choice. After the third dose, the albendazole was discontinued due to nausea, vomiting, and fever. The complaints ceased. Fifteen days after stopping the treatment, the patient was started on mebendazole to treat intestinal parasitosis. On the third day of mebendazole therapy, the patient complained of abdominal pain, nausea, and dark urine. Laboratory analyses showed elevated transaminases and elevated parameters of cholestasis. Immunological analyses showed significantly elevated IgG levels. Wilson disease, alpha-1 antitrypsin deficiency, and hemochromatosis were excluded, as acute hepatitis caused by hepatotropic viruses. Ultrasonography of the liver and biliary system was normal. Magnetic resonance cholangiopancreatography (MRCP) showed no intra and extrahepatic biliary tree changes. Treatment with corticosteroids (prednisolone 1 mg/kg) and ursodeoxycholic acid (20 mg/kg) was started.

Based on clinical and laboratory analyses, albendazole-induced DILI and albendazole-induced autoimmune hepatitis were considered. Based on the RUCAM score, which was 8, 'mixed' liver injury was most likely due to DILI [9]. Histopathological findings after a percutaneous liver biopsy revealed confluent necrosis around the central vein with mild lymphocytic infiltration. There were no signs of liver fibrosis nor interface hepatitis or rosette formation. As total IgG was elevated, immune-mediated DILI was diagnosed. Corticosteroid therapy led to a favourable clinical and laboratory response. Throughout further treatment, corticosteroids were gradually decreased and discontinued after 8 weeks. The patient was regularly monitored, initially monthly, and then quarterly. One year after corticosteroid cessation, transaminases, gamma-glutamyl transferase (GGT) and bilirubin were normal, as was total IgG. However, a significant increase in the titer of anti-smooth muscle

autoantibodies (SMA) to 1/80 was noted for the first time.

### Discussion

Liver damage caused by medication is one of the most common causes of liver injury. The exact incidence is unknown and existing data obtained in population studies is highly variable, most likely due to differences in data processing methods. However, it shows that the incidence is between 2.4-13.9 per 100,000. In the US and Europe, DILI is the most common cause of acute liver failure [1].

DILI can resemble liver damage from any other causes. It may occur while receiving treatment, but it can sometimes manifest even months after the discontinuation of medication; hence, a well-taken medical history is vital to reach a diagnosis, as well as additional laboratory testing [2].

Pathophysiologically, DILI occurs due to an intrinsic or idiosyncratic reaction. An intrinsic reaction is dose-dependent and occurs when the drug or its metabolite exceeds the toxic limit in hepatocytes. Onset is soon after the beginning of treatment, but it usually passes quickly once the medication is stopped, although it can also be fatal. It is expected and most commonly described with acetaminophen, cytostatic therapy, amiodarone, cocaine, aspirin, methotrexate, and herbal preparations with pyrrolizidine alkaloids [2]. For idiosyncratic reactions, hepatotoxicity is unpredictable, independent of dose and route of administration, and dependent on the patient individual characteristics [2]. The mechanism of idiosyncratic hepatotoxicity can be metabolic, due to the action of one of the compounds formed in the process of drug metabolism in the liver, or immune [1]. Immune-mediated DILI can be subdivided into two forms: DILI with autoimmune characteristics (AI-DILI) and immuno-allergic DILI (IA-DILI) [3].

Activation of the immune system in DILI is a complex, sometimes genetically determined process, and often is difficult to distinguish between drug-induced autoimmune hepatitis and immune-mediated DILI [3, 5]. It is crucial to consider clinical presentation and the course of the disease, immunological analyses, and histopathological changes in liver tissue [2]. Determining the HLA genotype can enhance both accuracy and confidence to distinguish DILI from AIH [10].

Immune-mediated DILI is most commonly associated with the use of minocycline and nitrofurantoin. The clinical course can take two directions: the gradual normalization of transaminases

after discontinuation of the drug, or a lack of improvement, which then requires immunosuppressive therapy. In this form, discontinuation of immunosuppressive therapy does not lead to relapse. However, drug-induced autoimmune hepatitis requires immunosuppressive therapy and, in this case, its discontinuation leads to relapse [2].

Independent of the mechanism, the drug or its metabolite can damage any cell in the liver (hepatocytes, cholangiocytes, stellate cells, or sinusoidal endothelial cells) and can cause acute, subacute, or chronic liver damage [4]. Acute DILI has three phenotypes: hepatocellular, cholestatic, and ‘mixed’. The phenotype is determined according to the R-value, which is obtained based on the ratio of ALT (U/L) to ALP (U/L) at the onset of illness. Hepatocellular damage is characterized by significant elevations of ALT, with normal or minimally elevated ALP, and R is  $\geq 5$ . With cholestatic damage, the elevation in ALP values is significantly higher, so R for this type of DILI is  $\leq 2$ . For the ‘mixed’ type, R is  $2 < R < 5$  [1,3].

The RUCAM score (Roussel Uclaf Causality Assessment Method) or CIOMS (Council for International Organizations of Medical Sciences) score is a standardized and validated method for assessing the likelihood that a particular drug, supplement, or herbal medication has caused liver injury [3,9]. In this assessment, the following are significant: a) the time that treatment with the medicinal product was started, b) the time hepatotoxicity was recorded, c) risk factors (age, alcohol consumption, pregnancy), d) exclusion of other causes of hepatotoxicity, e) the use of concomitant medicinal products that may lead to hepatotoxicity, f) whether there is already information on the hepatotoxicity of the medicinal product, and g) liver injury from reintroducing the medicinal product. Depending on the results, DILI is excluded ( $\leq 0$ ), unlikely (1–2), possible (3–5), probable (6–8), or highly probable ( $\geq 8$ ). [9] Despite its benefits, RUCAM also has its limitations. The score will be higher if the drug has previously been described as hepatotoxic or if the patient belongs to a risk group (people over 55, alcohol use, and pregnancy), which is a significant limiting factor for the paediatric population. In addition, in clinical practice, it is rare to decide to reintroduce a medicinal product that is suspected of having previously led to DILI [9].

In assessing the severity of DILI, in addition to levels of transaminases, alkaline phosphatase, GGT, and bilirubin, it is necessary to assess coagulation, encephalopathy, the involvement of other organ

systems, the risk of a fatal outcome, and the need for emergency liver transplantation [3].

The patient we presented had AI-DILI. According to the RUCAM score, it was the ‘mixed’ type of liver damage. Since IgG was elevated and AIH was considered a differential diagnosis, follow-up was indicated, especially when a significant titer of SMA was detected. According to the literature, there is just one published article on albendazole-induced autoimmune hepatitis in a pediatric patient. In this patient albendazole induced hepatotoxicity and elevation of IgG and ANA. After starting corticosteroids and azathioprine, rapid normalization of transaminases, IgG, and ANA [11]. Given the lack of long-term follow-up data, the question remains whether this patient had AI-DILI or whether albendazole initiated AIH.

## Conclusions

Albendazole is considered a relatively safe drug and is widely used in the treatment of parasitic infections. According to our knowledge, this is the first paediatric patient in the literature presented as AI-DILI. Due to the detected significant SMA titer, and since there is no data on whether albendazole can induce AIH, further monitoring of the patient is indicated.

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**Conflict of interests:** No conflict of interests is declared.