Recurrent albendazole-induced acute hepatitis

Janaína Luz Narciso-Schiavon, MD, 1*  Henrique Antonio Delziovo, MD, 1  Lucas Eduardo Benthien Santos, MD, 1  Maria Beatriz Cacese Shiozawa, MD, 2  Leonardo Lucca Schiavon, MD. 3

1. Núcleo de Estudos em Gastroenterologia e Hepatologia, Department of Internal Medicine, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil
2. Pathology Department, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil
3. Postgraduate Program in Medical Sciences, Health Sciences Center. Núcleo de Estudos em Gastroenterologia e Hepatologia, Department of Internal Medicine Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil.

*Correspondence: janaina.narciso@uol.com.br.

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Abstract
Albendazole is used to treat helminth infections and usually has minimal or no side effects. A transient increase in liver enzymes is common following its use, but little evidence of albendazole-induced liver damage has been reported in the literature. This study presents a patient who developed acute hepatitis following self-medication with albendazole. The patient also had a history of similar episodes in the past after using the drug. After a thorough investigation and exclusion of all other causes of the patient’s clinical condition, the Roussel Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences scale yielded a score of 10 points, indicating a high probability of albendazole-induced liver damage. In conclusion, expediting the process of combating helminths is ideal, but quality monitoring is required to avoid adverse reactions such as drug-induced hepatitis. Moreover, self-medication with any drug should always be discouraged.

Keywords
Drug-Induced Liver Injury; Albendazole; Alanine transaminase.

INTRODUCTION
Albendazole is a widely used drug in the treatment of parasitosis. Its effectiveness is proven against several species of parasites and it’s the treatment of choice for cysticercosis and hydatid disease in the United States. (1) It is also used to treat strongyloidiasis, taeniasis, ascariasis, hookworm, trichuriasis, oxyuriasis, among others. (1) The absorption of this drug is erratic and is better absorbed when consumed with fatty foods. (1-3) Albendazole is a prodrug that is converted into the active metabolite albendazole sulfoxide by first-pass metabolism in the liver, and its metabolites are excreted through the urine. (1, 2) Its effect is mediated by the inhibition of microtubule synthesis in the parasites’ cells. (1-5)

Albendazole’s side effects are rare, especially when administered for 1-3 days. When they do occur, they are usually mild. The most frequent side effects are epigastric discomfort, diarrhea, nausea, dizziness, headache, malaise, and insomnia. Prolonged therapy most commonly leads to adverse reactions, such as abdominal discomfort, headache, fever, fatigue, alopecia, increased liver enzymes, and pancytopenia. (1, 3, 4)

Reports of liver injury induced by albendazole are rare (6-14) and according to research, recurrent episodes are even rarer. (10-14) We herein report a case of recurrent hepatitis related to seasonal empirical use of albendazole.

CASE REPORT
A 36-year-old woman presented to the specialist doctor’s office with a “liver problem.” Three weeks earlier, she developed a fever of 38°C, myalgia, and sore throat. She also reported dark urine, nausea, and asthenia. She recalled self-medicating with albendazole before the onset of her symp-
toms and reported using this medication every summer. She had a history of insomnia and recurrent episodes of diarrhea, fever, malaise, myalgia, and jaundice for 3 consecutive years during the months of November and January. She denied smoking, alcohol use, blood transfusions, or use of illicit drugs. There was no family history of liver disease. Physical examination of the patient showed anicteric sclerae without the stigmata of liver disease; she had no asterixis. Laboratory tests revealed hemoglobin level of 12.8 g/dL, hematocrit of 38.7%, leukocyte count of 4,830/mm3, and platelet count of 180,000/mm3. Hepatic biochemical tests revealed the following results: aspartate aminotransferase (AST) = 1,304 U/L, alanine aminotransferase (ALT) = 2,220 U/L, alkaline phosphatase (ALP) = 158 U/L, gamma glutamyl transferase (GGT) = 123 U/L, total bilirubin = 5.89 mg/dL, direct bilirubin = 3.89 mg/dL, and prothrombin activity of 71%. Levels of ceruloplasmin (27.7 mg/dL), ferritin (145 μg/L), and transferrin saturation (49%) were normal. Anti-HAV IgG and IgM; HBsAg; IgM AntiHBc; and total anti-HBc, anti-HCV, and anti-HIV serology were negative. Tests for the following antibodies were negative: antinuclear antibodies, smooth muscle, anti-liver kidney microsomes 1, and anti-mitochondrial antibodies. Figure 1 shows the evolution of aminotransferase values to more than ten times the upper normal limit after the first exposure to albendazole. An exacerbation occurred 60 days after discontinuation of the drug, followed by progressive normalization. A new episode similar to the original appeared 10 months later after re-exposure (Figure 1). The patient underwent liver biopsy, which revealed minimal and unspecific reactive changes (Figure 2).

**DISCUSSION**

The diagnosis of acute hepatitis is confirmed by the presence of jaundice or non-specific symptoms of acute illness accompanied by elevation of AST and/or ALT activities. The best discriminant values for recognizing acute hepatic injury appear to be 200 U/L for AST and 300 U/L for ALT. Different etiologies have similar clinical presentation, such as hepatitis by hepatotropic virus, drug induced liver injury (DILI), autoimmune hepatitis, ischemic hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson’s disease, alcoholic hepatitis, cardiac and thyroid diseases, etc. However, serum aminotransferase levels 10 times greater than the upper limit of normal and with near-normal GGT levels restrict the differential diagnosis to some specific etiologies, including hepatitis by hepatotropic virus; DILI; autoimmune hepatitis; ischemic hepatitis; primary biliary cholangitis, primary sclerosing cholangitis, Wilson’s disease, alcoholic hepatitis, infectious causes, such as dengue, Epstein–Barr Virus, cytomegalovirus, toxoplasmosis.

DILI is a disease of variable clinical presentation, with a spectrum ranging from asymptomatic liver failure to chronic liver disease. It is a difficult condition to identify and its diagnosis is through exclusion, based on clinical
history, history of drug use and evaluation of the patient’s hepatic biochemical profile.\(^{(17, 18)}\)

The drug classes responsible for cases of DILI in a population differ according to the geographical location. In Western countries, the majority of cases are associated with antibiotics, anticonvulsants, and psychotropic agents. In Asia, on the other hand, herbal dietary supplements rather than conventional medications are the most common causes of DILI.\(^{(18)}\)

In younger patients, the hepatocellular pattern is more prevalent, and in older patients, cholestasis is more common.\(^{(19)}\) More than 17% of cases are attributed to idiosyncratic reactions, and liver failure is uncommon. There are no standardized and globally recognized ways to predict adverse reactions.\(^{(6)}\)

In this case, the patient in question was asymptomatic and had a history of self-medication with over-the-counter albendazole. Hookworm infections, for instance, are considered to be a leading cause of pathological blood loss in tropical and subtropical countries.\(^{(20)}\) Sanitation alone can control hookworm disease, however this method is extremely low.\(^{(20)}\) The administration of anthelmintics as preventive treatment and mass anthelmintic therapy are recommended in specific settings.\(^{(20, 21)}\) In the absence of adequate sanitation, the World Health Organization (WHO) advocates that anthelmintic treatment needs to be repeated every 6-12 months.\(^{(20)}\) However, these recommendations are not always followed, and the unrestricted and unsupervised use of an over-the-counter anthelmintic drug, at random dosages, can expose a subject to risky situations, such as the DILI. As reported in this study, albendazole can cause significant liver damage, and because the side effect is not trivial, albendazole-induced liver injury should always be considered by physicians when other causes have been excluded.

Teschke et al. performed a systematic review of 2906 cases of DILI \(^{(22)}\) and observed that 14% of the pre-
sumptive diagnoses of this condition were made without satisfactorily eliminating other possible etiologies. In this case report, the episodes of altered liver enzymes coincided with the period in which the patient used the medication. The possibility of viral hepatitis was ruled out by negative serology. Moreover, because of disease recurrence, the main differential diagnosis would be autoimmune hepatitis, which was also eliminated by the negative autoantibody test results and the biopsy report that demonstrated no significant liver damage. Although the patient’s laboratory tests did not follow the classical presentation, less likely causes were also excluded; accumulation diseases were excluded because of the normal levels of ceruloplasmin and ferritin. Also, the near-normal GGT values were not suggestive of cholestatic diseases.

As DILI is a diagnosis of exclusion, there are no absolute criteria or specific diagnostic methods to accurately diagnose this condition. Therefore, diagnostic scales are used for this purpose. The most commonly used scale is the Roussel Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences scale (RUCAM/CIOMS). (23-25) This scale rates the likelihood of a drug being related to the occurrence of liver injury according to the score obtained. In this case, the patient had a score of 10 points, which indicates a high probability that albendazole was the cause of her liver injury. Although transient increases in aminotransferase levels is a common adverse effect (approximately 10% of cases), (26-28) the prevalence of acute hepatitis due to this drug is rare.

CONCLUSION

Wariness of pre-formed concepts about numerous medicines considered innocuous is necessary, as exemplified in this case. This report is not meant to discourage empirical or non-bureaucratic administration of anthelmintic drugs by teachers, family members, or other non-health professionals, including those recommended by WHO in endemic areas. However, extrapolating this recommendation for low-prevalence areas, such as Southern Brazil,(29) may be, at least, incautious. Expediting the process of combating helminths is ideal; however, we must magnify the need for quality monitoring that avoids gaps that lead to adverse reactions, such as drug-induced hepatitis. Moreover, self-medication for any drug with harmful potential should always be discouraged.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES


