INTRODUCTION

Albendazole is an important broad spectrum anthelminthic used throughout the world, in the majority of instances in the brief therapy for intestinal nematodes. It has had an enviable low toxicity record. However, weeks to months of albendazole therapy have become common practice in the treatment of echinococcal and cysticercal infections. Metabolic and toxicity data for such prolonged therapies is slowly emerging. In this report, we describe a patient with hepatic cirrhosis who developed severe and prolonged pancytopenia following albendazole treatment of pulmonary echinococcosis. This is the third report of albendazole-induced pancytopenia in the literature, but the first to have lethal consequences.1,2 Benzimidazoles are metabolized by the liver. This metabolic process and the bone marrow toxic consequences of impaired liver function are reviewed here. They form the basis for our recommendation that alternatives to prolonged albendazole should be strongly considered in patients with compromised hepatic function.

CASE REPORT

The patient was a 68-year-old Peruvian man who lived in Canada for 20 years. In 1997, he was found to have Child-Pugh class B cirrhosis complicated by grade II esophageal varices. Based on a liver biopsy and negative serologies for hepatitis A, B, and C, cytomegalovirus, ferritin, ceruloplasmin, anti-nuclear antibody, and extractable nuclear antigen, a diagnosis of cryptogenic cirrhosis was made. Blood tests showed a serum albumin level of 34 g/L, an international normalized ratio (INR) of 1.12, and a platelet count of 103 × 10^9/L. Liver enzyme levels and function test results on admission were ALT = 29 U/L, alkaline phosphatase = 101 U/L, total bilirubin = 74 μmol/L, an increased INR (1.72), and a low albumin level (21 g/L). Serologies for hepatitis showed positivity for antibody to hepatitis B core antigen, but no evidence of active hepatitis, and his jaundice of recent onset was thought to be due to excess alcohol consumption. He was given vitamin K, metoprolol, and spironolactone and advised to stop alcohol consumption. He subsequently showed a loss of jaundice (bilirubin level = 56 μmol/L) and ascites, but a persistence of a low platelet count (118 × 10^9/L), an increased INR (1.5), and low serum albumin level (24 g/L).

A computed tomography (CT) scan of the lungs on this visit showed a 9-cm, fluid-filled cyst with an air fluid level of less than 10%, a crescent sign, and hyperdense layering in the dependent position described as sand. A diagnosis of a leaking echinococcal cyst was made and plans were made for surgical resection subsequent to four weeks of treatment with albendazole, 400 mg twice a day, which was to be monitored with measurement of serial liver enzyme levels. Prior to beginning treatment with albendazole, the patient’s complete blood count (CBC) was as follows (hemoglobin = 132 g/L, platelets = 118 × 10^9/L, white blood cell count = 5.96 × 10^9/L).

Sixteen days after starting treatment with albendazole, the patient presented to an emergency department complaining of not feeling well with a dry cough for four days. On arrival, he had a blood pressure of 60/40 mm of Hg, a pulse rate of 130 beats per minute, a temperature of 40.7°C, and a respiratory rate of 20/minute. Laboratory investigation indicated pancytopenia, with a hemoglobin level of 68 g/L, a white blood cell count of 0.05 × 10^9/L, a platelet count of 0.05 × 10^9/L, and 0 neutrophils, and a platelet count of 11 × 10^9/L. Liver enzyme levels and function test results on admission were ALT = 35 U/L, aspartate aminotransferase = 85 U/L, total bilirubin = 82 μmol/L, INR = 1.9, and albumin = 17 g/L (Table 1). A chest radiograph showed a considerably larger air fluid level within the lung cyst (Figure 1), and CT demonstrated an extensive right lung parenchymal infiltrate. The patient was admitted to the intensive care unit (ICU), where he was resuscitated with fluids, vasopressors,
and blood products. He was treated with meropenam and gentamicin for neutropenic sepsis, which was eventually confirmed by a blood culture growing *Klebsiella pneumonia*.

A peripheral blood smear showed low counts of all three cell lines with some spherocytes and giant platelets, but otherwise normal morphology. Tests results for anti-nuclear antibody, folate, ferritin, and vitamin B₁₂ were normal. Treatment with albendazole was stopped on admission to the hospital and replaced with praziquantel, 900 mg intravenously, twice a day. The patient was given granulocyte colony-stimulating factor and intravenous immunoglobulin for bone marrow stimulation, and amphotericin B was given for candidemia. Seven days following admission to the ICU, there was still no peripheral evidence of marrow recovery, and the patient remained on vasopressors and dependent on blood products. Rare hooklets were noted in a bronchial aspirate. On the ninth day of care in the ICU, the patient passed blood via the nasogastric tube, as well as massive amounts of maroon stool. He was transfused with 12 units of fresh frozen plasma, 20 units of cryoprecipitate, 12 units of platelets, and 15 units of packed red blood cells. However, the patient died following unsuccessful resuscitation.

Autopsy of the patient confirmed a 9.0-cm, right lower lobe echinococcal cyst containing protoscolices, and there was purulent inflammation around the cyst and in both bases, consistent with bilateral bronchopneumonia. Bone marrow examination showed slight hypocellularity on low magnification, and increased numbers of precursors of both the myeloid and erythrocyte cell lines, with few bands or mature neutrophils. There was a normal number of megakaryocytes, and no evidence of an infectious process or lymphoproliferative process in the marrow (Figure 2). It was concluded that the findings on bone marrow on autopsy were secondary to albendazole toxicity. The immediate cause of death was determined to be esophageal variceal bleeding.

### DISCUSSION

Albendazole is a benzamidazole used for treatment of human echinococcosis since the 1980s. It acts on β-tubulin to inhibit helminth microtubule formation.³ Prolonged, 2–4-week pre-operative and post-operative oral albendazole in the surgical treatment of echinococcal cysts or one-month medical therapy are now more frequently administered. Prolonged cyclical or continuous albendazole therapy for echinococcal cysts at a dose of 10–15 mg/kg produces cure rates ranging from 11.8% to 33.3%.⁴,⁵ Monitoring of liver enzyme levels is advised during this therapy.⁴,⁶,⁷

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Serial blood counts, liver enzyme levels, and INR*</th>
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<tbody>
<tr>
<td></td>
<td>At presentation</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>128</td>
</tr>
<tr>
<td>WBCs (×10⁹/L)</td>
<td>5.96</td>
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<tr>
<td>Platelets (×10⁹/L)</td>
<td>103</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>96</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>49</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>58</td>
</tr>
<tr>
<td>INR</td>
<td>2.27</td>
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*INR = international normalized ratio; WBCs = white blood cells; ALP = alkaline phosphatase; ALT = alanine aminotransferase.*
Albendazole has been used by millions of patients for a wide variety of parasitic diseases. Passive reporting of side effects to the manufacturer is very small, with leukopenia, reported as a rare complication, occurring in 0.044% of patients using albendazole as a single dose or for several days. Overall, the incidence of neutropenia in long-duration use has been reported as less than 1%. However, there are instances in which this incidence has been much higher. Neutropenia reached 33% in a phase 1 chemotherapy trial in which all patients had significant replacement of the liver with cancer. In another study of echinococcus treatment, 2 of 12 patients developed neutropenia. One of the two patients had complete biliary obstruction from echinococcal disease. There has also been an isolated case report of aplastic anemia in association with prolonged albendazole use in a patient with portal hypertension. This patient showed a rapid reversal of the hematologic anomaly on cessation of treatment with albendazole and supportive care. In animal studies, specifically in Wistar rats, large doses of albendazole (60–120 mg/kg/day) have been observed to systematically cause pancytopenia with marked loss of hematopoetic cells in the bone marrow.

Albendazole undergoes virtually 100% first-pass metabolism in the liver, and is rapidly converted to albendazole sulf oxide by both the microsomal flavin mono-oxidase and P450 CYP3A enzymes. It then undergoes partial further metabolism to albendazole sulfone via a separate P450-dependent enzyme CYP2C. Pharmacokinetic studies have demonstrated significant intra-individual and inter-individual variation in peak dose (Cmax) following albendazole ingestion among healthy volunteers. There are several known contributors to this variation. Modifications in bioavailability have been observed with the co-ingestion with a fatty meal, which more than triples the peak concentration (Cmax) of albendazole sulf oxide, as does grapefruit ingestion. While there are no published studies of albendazole pharmacokinetics specifically in individuals with cirrhosis, observations in individuals with extrahepatic obstruction have shown a doubling in the Cmax and an increased half-life (T1/2). Studies in healthy volunteers also demonstrate albendazole-induced hepatic oxidizing enzymatic induction with a reduced T1/2 and area under the curve in multi-dosing studies. Whether this occurs in patients with hepatic dysfunction is unknown.

The principal mode of action of the benzimidazole sulfides, such as albendazole and fenbendazole (mebendazole, thia-bendazole) is their inhibitory effect on tubulin polymerization, which results in the loss of cytoplasmic microtubules. Parent albendazole appears to be a much more potent inhibitor of tubulin polymerization than is albendazole sulfoxide and albendazole sulfone is inactive. Impairment of liver oxidase enzymes, such as occurs in hepatic failure, is likely to result in reduced conversion of albendazole to its sulfoxidation metabolites, high circulating levels of parent albendazole and, as a consequence of higher levels of inhibition of tubulin polymerization, result in a greater inhibition of microtubule-dependent processes such as cell division. This could result in bone marrow toxicity.

We hypothesize that the presence of significant hepatic dysfunction results in a reduced conversion of albendazole to albendazole sulfoxide and sulfone and a consequent significant circulation of parent albendazole. Because parent albendazole is a much more potent inhibitor of tubulin polymerization than the sulfoxide, this will increase the toxicologic effects on cellular functions dependent on microtubules.
OPATRNY AND OTHERS

with subsequent bone marrow toxicity in these patients. This is supported by both animal studies and the aforementioned published case reports in humans. There is no current recommendation for dose adjustment, increased monitoring, or consideration of alternative therapy in patients with hepatic failure. Measurement of albendazole levels as a means of routine monitoring is not feasible at this time because this is performed mainly in research settings, and is not widely available. Pharmacokinetic information, examination of our patient’s clinical course, as well as comparable cases in the literature suggest a reconsideration of the safety of albendazole therapy in patients with any hepatic dysfunction. Alternatives to prolonged albendazole therapy should be strongly considered in such patients. If albendazole remains the treatment of choice in such patients, very close serial monitoring of the CBC should be performed in addition to the existing recommendation of serial monitoring of liver enzyme levels. Should any indication of marrow toxicity occur, immediate cessation of the medication and close follow-up is warranted.

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REFERENCES