Emergency Liver Transplantation in Amodiaquine-Induced Fulminant Hepatitis

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Abstract. Amodiaquine is an amino-4-quinoline with the basic spectrum of activity of chloroquine. It has been used widely to treat and prevent malaria. From the mid-1980s, there were reports of fatal adverse drug reactions described in travelers using amodiaquine as antimalarial prophylaxis. In 1990, the World Health Organization (WHO) stopped using this drug in malaria control programs. The WHO Expert Committee on Malaria modified this in 1993 and reported that amodiaquine could be used for treatment if the risk of infection outweighs the potential for adverse drug reactions. Currently, amodiaquine is a potential useful drug, especially if used with artemisinin-based combination therapy and with sulfadoxine-pyrimethamine to improve treatment efficacy for chloroquine-resistant strains of Plasmodium falciparum and P. vivax. We report a case of fulminant hepatitis induced by antimalarial prophylactic use of amodiaquine that necessitated emergency orthotopic liver transplantation.

CASE REPORT

A 39-year-old woman living in Algeria who had a history of thyroid lobectomy for micro-follicular adenoma went to Benin on February 24, 2003 until May 29, 2003. She was taking amodiaquine, 200 mg, once a week, from February 24, 2003 until May 25, 2003, as antimalarial prophylaxis. On May 10, she started to feel dizzy and weak and had right hypochondral pains and nausea. Approximately 10 days later, she became jaundiced. Her symptoms worsened and she consulted a physician who diagnosed hepatitis A without any blood test and prescribed an anti-histamine H1, cyproheptadine chloride, and a day for approximately five days for headaches, and alprazolam, 0.5 mg a day in the evening for approximately 10 days. The patient had no history of alcohol intake and was vaccinated against yellow fever.

Her general condition worsened and she came to the University Hospitals of Geneva on May 29. On admission, she was afebrile, jaundiced, and weak. Clinical examination showed right hypochondral tenderness but no hepatosplenomegaly. Apart from asterixis, she had no other neurologic symptoms. Her liver enzyme levels were highly elevated: aspartate aminotransferase = 1,137 U/L (normal = 11–24 U/L), alanine aminotransferase = 1,475 (normal = 9–42 U/L), and γ-glutamyl transpeptidase = 124 U/L (normal = 9–35 U/L). Other biochemical test results were total bilirubin = 410 μmol/L (normal = 7–25 μmol/L), conjugated bilirubin = 204 μmol/L (normal = 2–9 μmol/L), and alkaline phosphatase = 108 U/L (normal = 30–125 U/L), prothrombin time = 17% (normal = 80–120%), factor V = 22% (normal = 65–130%), factors VII–X = 10% (normal = 80–120%), fibrinogen = 0.7 g/L (2.0–4.0 g/L), hemoglobin = 123 g/L (normal = 120–160 g/L), platelets = 206 × 10^11/L (normal = 150–350 × 10^11/L), and serum or plasma creatinine = 78 μmol/L (normal = 35–88 μmol/L).

Ultrasound results of the abdomen were normal. Laboratory test results for malaria parasites, hepatitis A, B, and C viruses, cytomegalovirus, and Epstein Barr virus were negative. Autoantibodies to liver kidney microsomes, smooth muscle enzymes, and mitochondria were absent. Results of genetic analysis of hepatic cytochrome P450 isoforms 2C8 (CYP2C8*2, CYP2C8*3, CYP2C8*4 and CYP2C8*5), 2C9 (2C9*1, 2C9*2, 2C9*3), 2D6, and 2E1 were normal.

Within approximately four days her liver enzyme levels decreased slightly, but the prothrombin time and factor V levels did not change. Her clinical condition deteriorated with the onset of stage II of hepatic encephalopathy (confusion and disorientation). She was immediately put on the waiting list for hepatic transplantation, and received a liver transplant on the sixth day of hospitalization. The operation was successful, she completely recovered, and was discharged on the 19th day of hospitalization.

Histologic analysis of the liver showed subtotal hepatic necrosis and lobular collapse associated with portal and lobular inflammation characterized by lymphocytes, eosinophils, and some neutrophils. There were rare hepatocellular nodules and neo-ductules compatible with regeneration. There was discrete chronic cholecystitis.

DISCUSSION

This fulminant hepatitis was classified as a reaction to amodiaquine according to the current World Health Organization criteria,1,2 and when the chronology of drug exposure, the anatomicopathologic results, the literature regarding amodiaquine-induced hepatitis, and the exclusion of other possible causes of fulminant hepatitis were taken into account. Jaundice was present before the administration of acetaminophen and cyproheptadine. Although low dosages were used, the role of these drugs in exacerbating the effects of amodiaquine could not be completely ruled out, and this opens an area for further research. The patient had no fever or any other symptoms suggestive of leptospirosis or yellow fever (she was vaccinated against yellow fever).

Amodiaquine has caused serious and, in some cases, fatal liver and bone marrow toxicity in travelers when used as prophylaxis.3–6 The reported rate of serious hepatic reaction is 1 in 15,650 amodiaquine users.4–6 Although amodiaquine-induced hepatitis is uncommon, it is serious and could lead to encephalopathy and death. The patient described herein survived only because of a liver transplant. A few cases of cytolitic hepatitis have occurred as early as three weeks after exposure. With the long half-life of amodiaquine (9–18 days), jaundice could persist for as long as 3–6 months. Liver test results remain abnormal approximately 7–27 months after the

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The pathogenesis of amodiaquine-induced hepatitis remains unclear. However, this drug may have a direct toxic effect on the liver through production of a quinone imino intermediate or through anti-amodiaquine IgG antibodies.

It has been reported that amodiaquine clearance and its metabolism to N-desethyl amodiaquine is mediated mainly by cytochrome CYP2C8 enzyme activity. The cytochrome P450-dependent mono-oxygenase system is the product of a multigene family of central importance in the metabolism of drugs. Genetic polymorphism is believed to play an important role in clinical toxicology for a number of cytochrome CYP subfamilies. The CYP2C subfamily constitutes a major group of expressed P450 in the human liver, with four isozymes identified (cytochrome P450 2C8, 2C9*10, 2C18, and 2C19). Genetic polymorphisms have been identified in all members of this subfamily. Because amodiaquine clearance and its metabolism to N-desethyl amodiaquine is mediated mainly by CYP2C8, our patient was genotyped for CYP2C8, 2C9*1, 2C9*2, and 2C9*3 variant alleles. She did not have any mutations. Single-nucleotide polymorphism of the CYP2C subfamily is unlikely to have contributed to this case of fulminant hepatitis, which suggests that a toxic metabolite of amodiaquine could have contributed to the cause of this disease.

Amodiaquine is more palatable and effective in the treatment of malaria than chloroquine. However, since the mid-1980s, there were reports of fatal adverse drug reactions described in travelers using amodiaquine as antimalarial prophylaxis. Since 1990, amodiaquine has not been recommended for malaria prophylaxis because of serious side effects, especially agranulocytosis and hepatotoxicity. However, its combination with sulfoxidine-pyrimethamine appears to be an effective treatment regimen for uncomplicated Plasmodium falciparum malaria in areas of low resistance to those drugs; even more effective is the combination amodiaquine and atesunate.

The patient in this case report was prescribed amodiaquine by her doctor in Algeria. This implies that some people are still being prescribed amodiaquine to prevent malaria. When they have similar signs and symptoms, they could be misdiagnosed as having malaria or viral hepatitis, which could result in liver failure that is not recognized as drug-induced. This supposition warrants further investigation, and education of physicians, pharmacists and the public to increase awareness of the potential risks of using amodiaquine as antimalarial prophylaxis.

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