Hepatitis Temporally Associated With an Herbal Supplement Containing Artemisinin—Washington, 2008

**ARTEMISININS ARE A CLASS OF COMPOUNDS** that include artesunate, artemether, and artemisinin and have potent antimalarial activity. In combination with other drugs (artemisinin combination therapy), these compounds are the first-line treatment recommended by the World Health Organization for Plasmodium falciparum infections. Artemisinins have been available in the United States without a prescription as herbal supplements for at least 10 years; these supplements are marketed for general health maintenance and for treatment of parasitic infections and cancers. On August 27, 2008, CDC was notified of a patient who developed hepatitis after a 1-week course of an herbal supplement containing artemisinin. The patient had abdominal pain, dark urine, and laboratory results consistent with hepatitis (e.g., serum alanine aminotransferase of 898 IU/L [normal: 10-55 IU/L]). Samples of the supplement were sent to CDC and the Georgia Institute of Technology for analysis to determine the amount of artemisinin and to identify any contaminants. Analysis indicated that the supplement contained 94%-97% of the 100 mg of artemisinin stated on the packaging and the supplement contained no other common pharmaceutical active ingredients. Given the patient’s clinical course and laboratory evaluation, CDC investigators concluded that the hepatitis might have been associated with ingestion of the herbal supplement containing artemisinin. More data are needed to establish any causal connection between artemisinin and hepatitis. Healthcare providers should be aware of the possibility of hepatic toxicity in patients taking herbal supplements containing artemisinin.

**Case Report**

On August 21, 2008, a man aged 52 years in Seattle, Washington, went to his primary-care physician with symptoms of severe fatigue and dark urine. His medical history included lactose intolerance and irritable bowel syndrome but no known hepatic dysfunction or alcohol abuse. His only medication was a multivitamin. Two weeks earlier, the patient had visited a naturopathic provider for long-standing abdominal discomfort that the provider attributed to a parasitic infection after stool studies reportedly showed an “unidentifiable protozoan.” The naturopathic provider had started him on a 6-week course of an herbal supplement containing 100 mg of artemisinin, two capsules orally three times a day, resulting in a dose of 7.5 mg/kg/day of artemisinin. The supplement was manufactured and sold through a company in the United States. Approximately 1 week into therapy, the patient developed worsening abdominal pain and dark urine. Three days later, on August 18, he stopped taking the supplement when his symptoms did not abate, and 3 days after that, he went to his primary-care physician.

Physical examination by the primary-care physician revealed mild scleral icterus and upper abdominal tenderness. The patient reported no fever, cough, diarrhea, or other symptoms. He reported no significant alcohol use, additional use of over-the-counter medications (e.g., acetaminophen), ill contacts, recent international travel, or exposure to unsafe food or water. Laboratory findings were consistent with hepatitis: a serum alanine aminotransferase of 898 IU/L (normal: 10-55 IU/L), aspartate aminotransferase of 280 IU/L (normal: 10-40 IU/L), bilirubin of 3.1 mg/dL (normal: 0.2-1.2 mg/dL), and alkaline phosphatase of 258 IU/L (normal: 40-150 IU/L). Five months earlier, on March 12, as part of an evaluation for inflammatory bowel disease, all laboratory values had been found within normal ranges.

Among laboratory findings on August 21, the following were within normal ranges: white blood cell count, hemoglobin, hematocrit, platelets, sodium chloride, serum creatinine, glucose, and calcium. The patient’s potassium (3.4 mmol/L [normal: 3.4-5.2 mmol/L]) and carbon dioxide content (22 mmol/L [normal: 22-31 mmol/L]) were borderline normal, and blood urea nitrogen was just below the normal range (8 mg/dL [normal: 9-25 mg/dL]). Laboratory analysis for hepatitis A antibody total and antibody IgM; hepatitis B core antibody, core antibody IgM, surface antigen, and surface antibody; and hepatitis C antibody all were negative. Laboratory testing detected no acetaminophen. Examination of the patient’s stool for ova and parasites was negative.

The patient was admitted to the hospital on August 21, for continued monitoring and supportive care and discharged home on hospital day 3. During the next 2 weeks, the patient’s liver function test results and symptoms gradually improved and had returned to normal by September 4.

**Herbal Supplement Analysis**

On September 8, two samples from the patient’s home supply of the herbal supplement were sent to CDC for analysis with high-performance liquid chromatography to determine whether the supplement contained 100 mg of artemisinin as stated on the packaging. Additional samples from the same bottle were sent to the Georgia Institute of Technology to identify any other clinically relevant...
organic contaminants by mass spectrometry. The CDC analysis indicated 94 mg and 97 mg of artemisinin in the supplement; no contaminants or additional organic active pharmaceutical ingredients were found in the other samples.

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**CDC Editorial Note:** Artemisinin (called qinghaosu in Chinese) is found in the leaves of *Artemisia annua* (the sweet wormwood shrub) and has long been used as an herbal treatment in China. Although widely used in herbal supplements of U.S. manufacturers, until recently artemisinins were not available for medical use in the United States except from CDC under an investigational new drug protocol. In April 2009, an artemisinin combination therapy, artemether-lumefantrine (Coartem [Novartis]), was approved by the Food and Drug Administration (FDA) for the treatment of malaria. Artemisinin-containing therapies generally are considered safe, effective, and well-tolerated medications for the treatment of malaria caused by *P. falciparum* with no major side effects. Although hepatic toxicity in humans has been reported from ingestion of a wide range of herbal preparations, a search of the literature revealed no previously published reports of hepatic toxicity from an herbal supplement containing artemisinin. However, FDA’s Center for Food Safety and Applied Nutrition has additional reports of adverse events involving ingestion of artemisinin-containing dietary supplement products that were not included in this review (FDA, unpublished data, 2009).

In the case described in this report, the patient’s presentation, history, and clinical course suggest that his hepatitis might have resulted from ingestion of an artemisinin-containing herbal supplement over a 10-day period. An investigation did not identify any other etiology for the hepatitis, and after the patient stopped taking the herbal supplement (7.5 mg/kg/day), a gradual but complete resolution of the patient’s signs and symptoms resulted. However, further study is needed to delineate any causal connection between artemisinin and hepatitis.

In a review of 108 trials of artemisinins involving 9,241 patients, only 0.9% had isolated elevated aspartate aminotransferase associated with artemisinin derivatives. Eleveted liver enzymes have been observed in patients treated for malaria with artemisinins but are generally thought to have resulted from the underlying malaria rather than the artemisinins. In other countries, the commonly recommended oral therapeutic dose of artesunate is 4 mg/kg/day for 3 days when used in combination with other drugs for treatment of acute malaria. Because the chemical structures of the artemisinins (i.e., artesunate, arteether, and artemisinin) are similar and they are metabolized into the same active compound in the body (dihydroartemisinin), the therapeutic window for these compounds are similar. Therefore, the 10-day regimen of artemisinin herbal supplement at 7.5 mg/kg/day described in this report is substantially more than the dosage of artesunate routinely used for treatment of malaria.

In laboratory testing, rats given 600 mg/kg/day of artemisinin for 7 days demonstrated slight degenerative changes in the liver, heart, spleen, lung, and kidney, and dogs given 100 mg/kg/day of artemisinin for 7 days had minimal observable physiologic effects. The only reports of hepatic toxicity caused by artemisinin compounds in laboratory animals were in guinea pigs exposed to 16 mg/kg/day of artesunate for 7 days and in rats exposed to 4 mg/kg/day of artesunate for 5 days. However, limitations exist in comparing animal ingestions of artemisinin with human ingestion of artemisinin, although they are closely related compounds.

FDA regulates herbal supplements under a different standard than food, over-the-counter medications, and prescription medications. Under the Dietary Supplement Health and Education Act of 1994, the manufacturer is responsible for ensuring the safety of a dietary supplement, and FDA takes action against unsafe supplements after they reach the market. Because federal regulation of dietary supplements differs from that for pharmaceuticals, potential concerns arise about quality control, recommended indications, and unsupervised usage. Herbal supplements also can potentially interact with other medications and reduce or potentiate their effects, which can include toxicity. Health-care providers should be aware that patients might be taking herbal supplements containing artemisinin and consider inquiring about their use in patients being evaluated for hepatitis without a clear etiology. Adverse events or illnesses thought related to the use of artemisinin-containing dietary supplements should be reported to FDA by telephone (1-800-FDA-1088) or via the Internet (http://www.fda.gov/safety/medwatch/howtoreport/ucm053074.htm). Additional information is available at http://www.fda.gov/food/dietarysupplements/alerts/ucm111110.htm.

**REFERENCES**

1. CDC. New medication for severe malaria available under an investigational new drug protocol. MMWR. 2007;56(1):76-77.