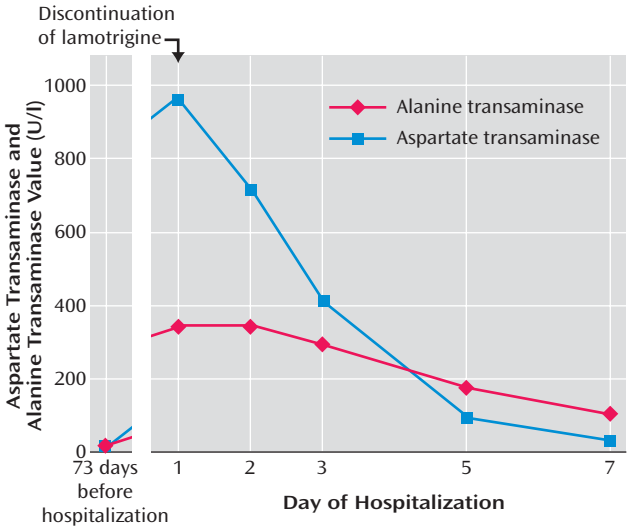
Acute Hepatotoxicity Associated With Lamotrigine

TO THE EDITOR: Lamotrigine, an antiepileptic medication, is indicated for maintenance treatment in bipolar I disorder (1). Elevated transaminases or hepatitis is reported as a rare side effect (less than 1/1,000 patients) (1). A literature review revealed 11 cases of acute hepatitis (2–10) attributed to lamotrigine, with two deaths (5, 7). A majority of these patients who developed elevated transaminases were concomitantly taking other liver-toxic medications, most specifically valproic acid. We report a unique case in which acute hepatitis occurred in a patient who was receiving lamotrigine in the absence of other medications.

A 21-year-old Caucasian male with a history of schizophrenia was admitted to our inpatient psychiatry unit for paranoid delusions. On admission, his medications consisted of lamotrigine (200 mg/day) and aripiprazole (15 mg/day), although his family reported nonadherence with aripiprazole. The patient's family insisted that he suffered from bipolar disorder and encouraged compliance with lamotrigine, which the patient later confirmed that he had been receiving prior to admission. The overall duration and dosage titration of lamotrigine was unknown, although the patient was taking lamotrigine (200 mg/day) 2 months prior to admission. On admission, his physical examination revealed no acute findings. However, his baseline laboratory examination revealed that he was experiencing acute liver failure, with elevated levels of aspartate aminotransferase (960 U/liter) and alanine aminotransferase (347 U/liter). Other laboratory results were normal, except for a slightly elevated white blood cell count of 13,300/mm^3, which normalized in 2 days. The patient was afebrile and showed no signs of infection. His liver function tests 2 months prior were normal (aspartate and alanine aminotransferase levels: 19 U/liter). The patient had no prior medical history, denied use of over-the-counter medications, and reported no history of alcohol or substance use except for ingesting a wild mushroom 1 month before, and he reported no acute effects after ingestion. In view of our assessment that the patient suffered from schizophrenia and because of elevated levels of aspartate and alanine aminotransferase found in his liver function tests, lamotrigine was not restarted on admission. Serology tests for hepatitis A, B, and C and Epstein-Barr were negative. Autoimmune tests for antimitochondrial antibodies, antismooth muscle antibodies, and antinuclear antibodies were also negative. Within 5 days of discontinuing lamotrigine, the patient's aspartate aminotransferase levels returned to the normal range, and alanine aminotransferase levels remained mildly elevated at 102 U/liter (Figure 1). During admission, the patient was restarted on aripiprazole, and the dosage was increased to 25 mg daily. He was stable on hospital day 7 and discharged to go home while receiving treatment with aripiprazole.

According to the Naranjo Probability Scale (11) for adverse drug reactions, it is probable that lamotrigine was the cause of acute hepatoxicity in our patient. The close temporal relationship between the initiation of lamotrigine and elevation of transaminases followed by the rapid decline in liver enzymes after lamotrigine was withdrawn also favors the diagnosis of lamotrigine-induced hepatitis. In addition, other causes (e.g., viral, alcohol) were excluded.

FIGURE 1. Time Course of Serum Liver Enzymes in Relationship to Lamotrigine Use



Our case differs from other reported cases (2–5, 7–10) in that lamotrigine was the only medication the patient was taking at the time of liver injury. Although the patient had been prescribed aripiprazole prior to admission, both the patient and his family confirmed his nonadherence to aripiprazole treatment. In addition, his liver enzymes continued to decrease after aripiprazole was restarted in the hospital. Although there are case reports of mushrooms causing fulminant liver failure, symptoms (e.g., vomiting, diarrhea, abdominal pain, and elevated liver function test) typically occur within the first 24 hours after ingestion (12). Our patient reported no symptoms after the one-time ingestion of a wild mushroom.

The mechanism of lamotrigine-induced liver failure that occurred in our patient is not clearly understood. Previous case reports, some with histopathologic findings, have attributed this reaction to an immune-mediated allergic reaction (4, 6–8). The titration method for lamotrigine in our patient is unknown. He reported compliance with lamotrigine treatment several weeks prior to admission; however, it is unknown whether he was compliant prior to the 2 weeks before admission. Rapid dose increase may have occurred, resulting in acute liver injury. However, the patient showed no signs of rash.

The use of lamotrigine in psychiatry has increased significantly after its approval by the Food and Drug Administration for maintenance therapy in bipolar I disorder. In the presence of elevated liver function tests, clinicians should consider lamotrigine as a potential cause.

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The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07050728) was accepted for publication in August 2007.