Fatal Hepatotoxicity Induced by Hydralazine or Labetalol

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Antihypertensive agents have been associated with adverse reactions that, if unrecognized by health practitioners, may have devastating consequences. The pattern of hepatotoxicity observed during therapy with the vasodilator hydralazine is highly variable, often making its diagnosis difficult. Serious hepatic injury induced by the α- and ß-adrenergic receptor antagonist labetalol has only recently been reported and therefore, many clinicians may be unaware of this adverse effect. Familiarity with the clinical features and course of hydralazine- and labetalol-induced hepatic injury is necessary to ensure prompt recognition and discontinuation of the agent.
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In general, the risk of life-threatening adverse effects posed by antihypertensive agents is minimal relative to the known complications of long-term uncontrolled hypertension.[1] Yet, antihypertensive agents have been associated with adverse reactions that can have devastating consequences if they are not recognized. The pattern of hepatotoxicity observed during therapy with the vasodilator hydralazine is highly variable, making its definitive diagnosis difficult.[2] Serious hepatic injury induced by the α- and ß-adrenergic receptor antagonist labetalol has only recently been reported,[3, 4] and therefore, many clinicians may be unaware of this complicaton.

Case Report

A 73-year-old man with a history of hypertension, gout, and hyperlipidemia had controlled his blood pressure well for many years with reserpine and furosemide. In November 1987, blood pressures were elevated and hydralazine was initiated. Control remained suboptimal, and enalapril was substituted for the reserpine. In January 1988 enalapril was discontinued and labetalol was prescribed. Two months later the patient first related complaints of anorexia and dark urine of 3 days' duration. Jaundice and hepatomegaly were noted on examination. Results of liver function tests were markedly elevated (Table 1), although they had been normal 13 months previously. The patient had no history of fever, chills, alcohol or intravenous drug abuse, prior liver disease, recent travel, or blood transfusions. Medications at the time consisted of labetalol 200 mg twice daily, hydralazine 50 mg 4 times daily, furosemide 20 mg once daily, gemfibrozil 300 mg twice daily, and probenecid 500 mg once daily, all taken by mouth. On March 23, 1988, the patient came to a local emergency room with grade IV encephalopathy. All medications were discontinued, and hydration, vitamin K, and lactulose were initiated. Laboratory values indicated severe hepatocellular damage.

The patient was transferred to University Hospital on the following day for further evaluation of his acute liver failure. Ultrasonography revealed no focal lesions or evidence of obstruction. Antinuclear antibody, hepatitis A IgM antibody, hepatitis B surface antigen, and hepatitis B core and surface antibodies were negative. Liver function continued to deteriorate, and renal failure developed over the next 5 days. The patient remained encephalopathic and died on March 29, 1988, 2 weeks after the onset of symptoms.

Liver biopsy performed at autopsy showed broad stretches of bridging and multilobular collapse containing pigmented macrophages. The remaining hepatic parenchyma appeared severely cholestatic with regenerative changes. In addition, there were scattered necrotic liver cells and slight

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Table 1. Results of Liver Function Tests[a]

Date	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)	Alkaline Phosphatase (IU/L)	Lactic Acid Dehydrogenase (IU/L)	Bilirubin (mg/dl)	Albumin (g/dl)	Prothrombin Time (sec)
2/3/87	21	18	134	136	—	—	—
3/18/88	4230	4590	346	1680	—	—	—
3/23/88	4400	3510	—	774	26.0	—	—
3/24/88	1748	2517	326	441	26.1	3.5	25.7
3/25/88	1560	156	356	452	32.0	—	—
3/26/88	1120	2165	323	469	34.5	3.5	24.3
3/27/88	675	2145	296	357	30.0	2.4	—
3/28/88	329	970	278	376	34.0	2.8	20.0
3/29/88	251	780	278	483	38.0	2.9	20.9

[a]Normal ranges: aspartate aminotransferase 2–35 IU/L; alanine aminotransferase 0–45 IU/L; alkaline phosphatase 30–130 IU/L; lactic acid dehydrogenase 60–200 IU/L; bilirubin 0.1–0.9 mg/dl; albumin 3.5–4.9 g/dl; prothrombin time 10–13 sec.

sinusoidal lymphocytosis. The process appeared to be 2–3 weeks old, but a specific etiology could not be established. Postmortem examination revealed a liver of normal size (1000 g) with numerous punctate hemorrhages in the parenchyma; all vessels were patent. The gallbladder and biliary tract were normal.

Discussion

Demonstrating a drug to be the cause of an adverse reaction relies on knowledge of the agent's safety profile, confirmation of a temporal relationship between initiation of the agent and production of symptoms, and exclusion of other potential etiologies.[2, 5] Ideally, improvement in symptoms with drug discontinuation and a positive rechallenge (i.e., the reappearance of symptomatology after reexposure to the drug) are elicited. Many times, however, these conditions are not fully satisfied, and establishing a conclusive etiology becomes difficult.

The known hepatotoxic potential of labetalol and hydralazine, as well as the time course of the reaction, implicate one of these agents as the cause of the liver failure in this patient.[5] Symptoms of hepatic injury were first evident 2 and 4 months after initiation of labetalol and hydralazine, respectively. All other medications (furosemide, gemfibrozil, probenecid) had been taken for many years without ill effects. In usual dosages they are not usually associated with serious hepatic injury, although probenecid was implicated in one case of fatal hepatitis.[2] Angiotensin-converting enzyme inhibitors are also uncommon causes of liver injury; however, acute hepatitis induced by enalapril was described in two patients after 10 days and 7 weeks of therapy.[6, 7] In this patient, enalapril was discontinued 2 months prior to the onset of clinical symptoms, which continued to progress, making that drug an unlikely cause of the reaction.

Clinical and histologic evidence of drug hepatotoxicity often resembles that produced by viruses.[8] In this man, hepatitis serologies were negative, and cytomegalovirus and Epstein-Barr virus antibody titers did not indicate acute infection. Due to the lack of specific diagnostic tests, the possibility of infection with non-A, non-B hepatitis cannot be excluded definitively, however, other clinical findings consistent with a viral illness were not apparent. There was no lymphocytosis; the patient remained afebrile, and white blood cell count and differential were within normal limits until 3 days before he died.

The mechanisms of idiosyncratic adverse drug reactions can be divided into those of an immunologic (hypersensitivity) origin and those due to a metabolic abnormality, in which drug or metabolites accumulate and exert toxicity.[8] Both hydralazine[9–12] and labetalol[13, 14] may induce a lupus-like illness accompanied by detectable antinuclear antibodies. Liver disease has been associated with this syndrome in patients treated with hydralazine.[9, 10] In this patient the negative antinuclear antibody titer and the absence of arthralgias, fever, rash, and eosinophilia made an immune-mediated process unlikely.

Rather, hepatic injury may have resulted from an idiosyncrasy in drug metabolism. Liver disease unaccompanied by lupus-like symptoms has occurred during therapy with hydralazine[15–21] and labetalol.[3, 4] The rate of hepatic acetylation, the major route of biotransformation of hydralazine, is genetically determined, and the risk of developing the lupus-like syndrome is directly correlated with slow acetylator status.[22] The possibility of a similar relationship between acetylator status and liver injury has been suggested, however, hydralazine-induced hepatitis was reported in a rapid acetylator.[18] In addition, although lupus-like manifestations were generally absent, some patients did have fevers, rashes, or eosinophilia, indicating a more complex pathogenetic mechanism.[15, 16, 21]

The course of the reaction and available studies support the possibility of hydralazine-induced hepatitis in this patient. The onset of symptomatic hydralazine hepatotoxicity varies from early, within 2–14 days of drug initiation,[17, 18, 21] to late, after 2 months to 3 years of therapy.[15, 16, 19] Hepatocellular necrosis and mixed hepatocellular-cholestatic hepatitis[15–20] are most frequently noted, although isolated cholestatic hepatitis has been observed.[21] Histologic analyses have revealed various patterns of injury, including granulomas,[20] bridging necrosis with lobular collapse and inflammatory cell infiltration,[16, 17, 19] and cholestasis.[19, 21] Unlike hydralazine-induced lupus, the reaction develops at a relatively low dosage of 50–150 mg daily and is usually reversible after drug withdrawal. Rechallenge with hydralazine in three patients resulted in rapid recurrence of symptoms.[15–17]

The potential for labetalol to induce hepatic dysfunction was recently emphasized by the drug's manufacturers in a letter to 285,000 physicians (written communication, Schering Corporation and Glaxo Inc., June 5, 1989). In addition, the prescribing information was revised to reflect the serious nature of these reactions and the importance of monitoring liver function tests in patients receiving the drug.[23, 24] According to data from clinical trials, approximately 4% of patients treated with labetalol may have increases in serum transaminase concentrations in excess of 3 times the upper limit of normal.[23, 24] In 74% of these patients, the levels decreased with continued therapy or after drug withdrawal. However, the manufacturers' recommendations are that labetalol be discontinued promptly and not restarted if laboratory or clinical evidence of liver injury is documented.

The first published report described a 63-year-old hypertensive woman with fatal hepatic failure induced by labetalol.[3] Clinical findings consistent with liver disease were initially noted after 2.5 months of labetalol 100–200 mg/day. A specific etiology was not identified, but liver function improved over 4 weeks after the patient independently discontinued the drug. During a follow-up visit, labetalol was again prescribed; symptoms of hepatic disease were apparent 2 months later. After 2 more months of therapy the drug was discontinued, however, hepatic function continued to deteriorate and the patient subsequently died. Hepatocellular necrosis with extensive multicellular collapse and fibrotic tissue surrounding scattered regenerating nodules were observed on postmortem examination of the liver.

Subsequent to this report, the Food and Drug Administration evaluated all submitted reports of hepatotoxicity in patients taking labetalol.[4] A causal relationship between the drug and liver disease was thereby established in an additional 10 patients, 2 of whom died as a result of the reaction. Hepatotoxicity was noted after a median of 60 days (range 21–189 days) of labetalol therapy with an average daily dose of 285 mg. Indicators of a hypersensitivity reaction were uncommon; none of the patients experienced elevated temperature, but a maculopapular rash and mild eosinophilia were documented in one patient each. Histologic data were available in four patients and were similar to those reported previously.[3] Varying degrees of hepatocellular necrosis with cellular infiltrates and, in one patient, cholestasis were observed.

This hepatic injury parallels that of the current patient. There was a 2-month interval between initiation of labetalol and the onset of symptoms, and the patient exhibited no signs of an allergic reaction. Features of the histologic studies were also similar: extensive hepatocellular damage with multilobular collapse and cellular infiltrates.

As of April 1989, there were 90 reports of hepatitis and hepatic necrosis, jaundice, and elevated liver function tests associated with short- and long-term labetalol therapy (written communication, Schering Corporation and Glaxo Inc., June 5, 1989). Nine of these patients, including the one described here, died.

The mechanism of liver injury associated with labetalol is unclear; however, as with hydralazine hepatotoxicity, it is postulated that affected patients may have altered metabolic capacities.[3] The clearance of debrisoquin correlates with the activity of drug oxidation mediated by the cytochrome P-450 system, an elimination route of the ß-adrenergic receptor antagonists.[25] Less than 10% of the population metabolizes debrisoquin poorly,[25] which may explain the low frequency of hepatotoxicity associated with ß-blocking agents. Metoprolol, a ß-blocker with metabolism similar to that of labetalol, was implicated in one case of hepatotoxicity, however, studies revealed that patient was an extensive metabolizer of debrisoquin.[26] Currently, no published data report the debrisoquin clearance status of patients with labetalol-induced liver damage.

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