

Nefazodone-Induced Liver Failure: Report of Three Cases

Jaime Aranda-Michel, MD; Alison Koehler, MD; Pablo A. Bejarano, MD; John E. Poulos, MD; Bruce A. Luxon, MD; Chaudhary Mobin Khan, MD; Looi C. Ee, MD; William F. Balistreri, MD; and Fredrick L. Weber Jr., MD

Background: Liver failure is a rare but devastating result of drug toxicity.

Objective: To describe three cases of subfulminant liver failure that were probably caused by nefazodone, a new antidepressant that is a synthetically derived phenylpiperazine.

Design: Case series.

Setting: Two university medical centers and a children's hospital.

Patients: Three women 16 to 57 years of age.

Intervention: Two patients underwent liver transplantation; the third was listed for transplantation but subsequently improved.

Measurement: Liver biopsy.

Results: Nefazodone was administered for 14 to 28 weeks before the onset of symptoms. The duration of jaundice before onset of encephalopathy ranged from 4 to 6 weeks. All cases of liver failure had similar histologic appearance, with prominent necrosis in the centrilobular areas (zone 3). One patient had successful liver transplantation, one underwent transplantation but died, and one improved without transplantation. The temporal onset of disease after the start of nefazodone therapy suggested severe hepatocellular injury caused by the drug.

Conclusions: Because nefazodone seems to cause severe hepatocellular injury in an idiosyncratic manner, routine liver chemistries should be performed before starting nefazodone therapy and patients should be monitored regularly. Therapy should be discontinued if liver enzyme concentrations become abnormal.

Nefazodone (Serzone, Bristol-Myers Squibb, Princeton, New Jersey), a new antidepressant, is a synthetically derived phenylpiperazine. The drug acts as a selective 5-HT₂-receptor antagonist and inhibits the presynaptic reuptake of serotonin and norepinephrine (1, 2). These pharmacologic properties of nefazodone differ from those of other antidepressants, such as tricyclics, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. Although nefazodone is structurally similar to trazodone, the two drugs differ pharmacologically and clinically. Unlike trazodone, nefazodone has an affinity for 5-HT-1A uptake sites and less potency for α_2 -adrenergic binding sites. In addition, nefazodone inhibits the presynaptic reuptake of norepinephrine in vitro (3). Because of these properties and because it is generally well tolerated and effective, nefazodone is an attractive antidepressant. However, we describe three cases of subfulminant liver failure that we believe were caused by nefazodone.

Patient 1

A 54-year-old woman was admitted to the University of Cincinnati Medical Center on 18 December 1996 with liver failure. Eight months before admission, she had begun therapy with nefazodone, 100 mg orally twice daily, for depression and clonazepam (Tranxene, Abbott Laboratories, Abbott Park, Illinois) for anxiety. She first noticed fatigue and intermittent nausea approximately 6 weeks before admission. She was seen by her family physician at that time, who noticed jaundice and discontinued both clonazepam and nefazodone therapies. The jaundice persisted, and 6 weeks later, she developed confusion. At that point, she was admitted to the University of Cincinnati Medical Center for consideration of liver transplantation. Her medical history included depression, anxiety, hypothyroidism, and hypertension. She reported no suicidal ideation; exposure to toxic substances, viral hepatitis, or blood products; intravenous drug use; getting a tattoo; alcohol use; or history of liver disease. Her only medication, in addition to nefazodone and clonazepam, was levothyroxine (Synthroid, Knoll Pharmaceuticals, Mount Olive, New Jersey), which she had been taking for several years.

On admission, the patient had jaundice and as-

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From University of Cincinnati and Children's Hospital Medical Center, Cincinnati, Ohio; and St. Louis University, St. Louis, Missouri. For current author addresses, see end of text.

Table. Laboratory Characteristics

Characteristic	Patient 1*	Patient 2*	Patient 3*
Duration of nefazodone therapy before symptom onset, <i>wk</i>	28	14	25
Time between onset of jaundice and discontinuation of nefazodone therapy, <i>d</i>	1	2	7
Duration of jaundice before onset of encephalopathy, <i>wk</i>	6	2.5	4
Alanine aminotransferase level, <i>U/L</i> †	2040	1345	1626
Aspartate aminotransferase level, <i>U/L</i> ‡	1760	1296	955
Alkaline phosphatase level, <i>U/L</i> §	97	206	273
Total bilirubin level, $\mu\text{mol/L}$ (<i>mg/dL</i>)	581.4 (34.0)	384.75 (22.5)	201.78 (11.8)
Albumin level, <i>mg/dL</i> ¶	2.1	4.3	3.0
Prothrombin time, <i>sec</i> **	29	25.2	13.4
International normalized ratio	2.9	2.5	1.3
Outcome	Died after orthoptic liver transplantation	Alive after orthoptic liver transplantation	Listed for orthoptic liver transplantation; condition improved before procedure was done

* In all patients, history and laboratory testing excluded other causes of liver disease. These included testing for hepatitis C virus (by enzyme-linked immunosorbent assay), hepatitis C virus RNA (by polymerase chain reaction), hepatitis A virus IgM antibody, hepatitis B surface antigen, hepatitis B core antibody, ceruloplasmin, α_1 -antitrypsin, antinuclear antibody, antimitochondrial antibody, anti-smooth-muscle antibody, cytomegalovirus IgM antibody, and Epstein-Barr virus viral capsid IgM antibody. No patient had a history of use of herbal medications or significant use of over-the-counter medications.

† Normal level, 7–46 U/L.

‡ Normal level, 11–35 U/L.

§ Normal level, 46–139 U/L.

|| Normal level, 3.42–20.52 $\mu\text{mol/L}$ (0.2–1.2 *mg/dL*).

¶ Normal level, 3.5–4.5 *mg/dL*.

** Normal time, 9.2–11.6 *sec*.

terixis and her sense of time was disoriented. She had no stigmata of chronic liver disease. The liver span was 6 cm, and there was no splenomegaly. Laboratory tests and their results are shown in the **Table**. Magnetic resonance imaging of the abdomen showed a small liver with a volume of 865 mL, patent vessels, no evidence of mass lesions, and minimal ascites. Transjugular liver biopsy was performed (**Figure, part A**). The patient was listed for liver transplantation and received supportive therapy, including lactulose, antibiotics, vitamin K, and blood products. Steroid therapy was not given. Her encephalopathy progressed to stage IV coma, and she developed hepatorenal syndrome, worsening coagulopathy, and gastrointestinal bleeding before an organ became available. She underwent liver transplantation on 30 December 1996, but she had a protracted hospital course with progressive renal failure, sepsis, and recurrent gastrointestinal bleeding. The patient died on 5 March 1997.

Patient 2

A 16-year-old girl was admitted to Children's Hospital Medical Center in Cincinnati, Ohio, on 12 June 1997 with liver failure. In February 1997, she began to take nefazodone, 200 mg orally twice daily, for depression. Fourteen weeks later, she developed nausea, vomiting, fatigue, and jaundice; nefazodone therapy was discontinued. One week later, she was admitted to a local hospital for persistence of these symptoms. Laboratory tests and their results are shown in the **Table**. Findings on abdominal ultra-

sonography were normal. She developed progressive confusion 2.5 weeks after the onset of jaundice. The patient was transferred to Children's Hospital Medical Center on 12 June 1997 for consideration of liver transplantation. On admission, she was jaundiced and somnolent and her sense of time was disoriented. She had no asterixis or stigmata of chronic liver disease. She had mild folliculitis on her chest. The liver span was 8 cm, and there was no splenomegaly, ascites, or peripheral edema. Laboratory examination showed a progressive decrease in aminotransferase and albumin levels along with an increase in bilirubin level and prothrombin time despite intravenous administration of vitamin K. She was initially given supportive care; this included daily intravenous methylprednisolone (Solu-Medrol, Upjohn Pharmacia, Kalamazoo, Michigan), 60 mg; lactulose; and daily antioxidant therapy with vitamin E, 1340 IU, *N*-acetylcysteine, 4690 mg, through a nasogastric tube every 4 hours, and intravenous infusion of prostaglandin E₁, 0.4 $\mu\text{g/kg}$ of body weight per hour. She was listed for liver transplantation, and her condition continued to deteriorate with worsening hepatic encephalopathy, coagulopathy and cerebral edema. She underwent cadaveric liver transplantation on 16 June 1997. The histologic features of the explanted liver are shown in part C of the **Figure**. The patient was alive and doing well at 10 months after liver transplantation.

Patient 3

A 57-year-old woman was receiving nefazodone, 100 mg orally twice daily, for depression. Twenty-

four weeks after the start of nefazodone therapy, she noticed increasing fatigue, decreased appetite, arthralgias, pruritus, dark urine, and clay-colored stools. Her primary physician diagnosed a urinary tract infection, and clarithromycin therapy was started. Forty-eight hours later, the patient noted jaundice and was admitted to a local hospital with fatigue, myalgias, and jaundice; at that point, nefazodone therapy was discontinued. The laboratory tests performed and their results are included in the **Table**. Liver biopsy was performed (**Figure, part D**). The patient was transferred to St. Louis University Medical Center on 13 February 1998 with grade 1 encephalopathy, weakness, jaundice, and ascites. Treatment with intravenous Solu-Medrol, 40 mg; lactulose; vitamin K; and ursodeoxycholate, 300 mg orally twice a day was initiated. Liver biopsy was repeated (**Figure, part E**), and the patient was listed for liver transplantation as status 2b. Subsequently, her mental status and chemistry results improved, and she was discharged while receiving oral prednisone, 30 mg/d; ursodeoxycholate, 300 mg orally twice daily; and oral furosemide, 20 mg/d. Two months after discharge, the patient improved sufficiently to be removed from the transplantation list.

Histology

Microscopic examination of the liver tissues from the three patients showed similar histologic findings (**Figure**). The initial injury occurred in the centrilobular area (zone 3), where there was collapse of the architecture with apoptosis and confluent necrosis. Diffuse hydropic degeneration (ballooning) of the hepatocytes was also present. The confluent areas of cellular loss extended from the center of the lobule to portal tracts. Progression of injury was evident, with formation of parenchymal nodules surrounded by fibrosis indicative of cirrhosis in patient 1. In addition, the periportal hepatocytes displayed pseudoglandular transformation (ductular proliferation) around areas of canalicular cholestasis. Lymphocytes infiltrated the bands of necrosis and fibrosis as well as the portal tracts and viable parenchyma. The interlobular bile ducts were not damaged, and the hilar blood vessels of the explanted liver specimens were not thrombosed.

Discussion

We report three cases of subacute liver failure that we believe resulted from severe hepatocellular injury due to nefazodone therapy. All three patients had negative results on investigations for other causes of acute liver injury, and the drug was

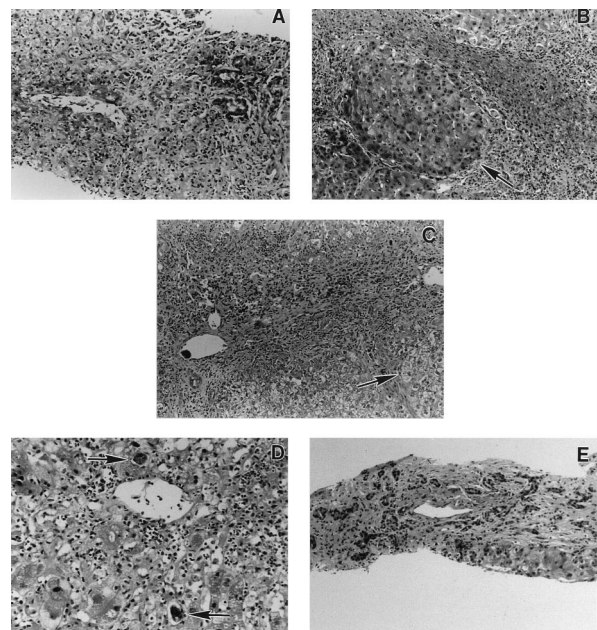


Figure. **A. Patient 1.** Initial biopsy specimen showing submassive centrilobular (zone 3) necrosis with collapse of the hepatic framework and adjacent ductular proliferation with cholestasis. (Hematoxylin–eosin; original magnification, $\times 200$.) **B. Patient 1.** Specimen from explanted liver 11 days after transplantation. Areas of confluent necrosis and congestion can be seen, and cirrhotic nodules had developed (arrow). (Hematoxylin and eosin; original magnification, $\times 100$.) **C. Patient 2.** Specimen from explanted cirrhotic liver with extensive centrilobular necrosis and lobular collapse with cholestasis and ductular proliferation. Ballooning of hepatocytes (arrow) is accompanied by lymphocyte infiltrates. (Hematoxylin–eosin; original magnification, $\times 200$.) **D. Patient 3.** Initial biopsy specimen with centrilobular hepatocyte ballooning and dropout of hepatocytes with apoptotic bodies (arrows). (Hematoxylin–eosin; original magnification, $\times 200$.) **E. Patient 3.** Specimen from repeated biopsy 12 days later, showing progression towards bridging fibrosis between central veins and associated bile-duct proliferation. (Hematoxylin–eosin; original magnification, $\times 200$.)

thought to be the most likely cause. All three patients also had a similar pattern of histologic injury with proximal centrilobular collapse and necrosis that made an autoimmune process unlikely. An unidentified viral agent remained a possible cause. Patient 1 was also taking clorazepate (Tranxene) for anxiety attacks. This triazolobenzodiazepine has been associated with mild elevation of liver enzyme levels (4, 5), but no cases of severe liver damage associated with this drug have been reported. The onset of symptoms after the start of nefazodone therapy ranged from 14 to 28 weeks, and the time from onset of jaundice to encephalopathy was 2.5 to 6 weeks. These cases therefore fit the clinical pattern of subfulminant hepatic necrosis caused by a drug (6, 7). Nefazodone therapy was discontinued promptly (within 2 to 7 days of the onset of symptoms), but all patients developed encephalopathy. Liver toxicity led to liver transplantation in patients 1 and 2, and patient 3 was listed for transplantation.

Nefazodone undergoes substantial first-pass metabolism by the liver, where it is metabolized by *N*-dealkylation and aliphatic and aromatic hydroxylation into three active metabolites: hydroxynefaz-

odone, triazolodone, and methylchlorophenylpiperazine (8, 9). Nefazodone is metabolized by cytochrome P450 3A4 but is also an inhibitor of this enzyme. Thus, other drugs that affect P450 3A4, such as ketoconazole, itraconazole, and erythromycin, may delay nefazodone clearance. In contrast, drugs that induce P450 3A4, such as carbamazepine and rifampin, may increase nefazodone clearance. Nefazodone can also increase levels of other drugs, including terfenadine, astemizole, alprazolam, triazolam, and cisapride, by direct inhibition of P450 3A4. Nefazodone is contraindicated in patients taking astemizole, terfenadine, or cisapride. Patients with liver cirrhosis may have higher levels of nefazodone metabolites because of decreased drug clearance (9). Premarketing evaluation of nefazodone found infrequent abnormal liver function tests. Hepatitis was rarely found, and fulminant or subfulminant hepatic failure was not reported (10).

To our knowledge, these three cases represent the first reports of subacute liver failure attributable to nefazodone. Liver failure has not been reported to the U.S. Food and Drug Administration. Although the interactions of nefazodone with other substances are well established, direct liver toxicity caused by nefazodone has not been described. The hepatotoxicity seen with nefazodone probably represents an idiosyncratic drug reaction, and a metabolite of nefazodone probably mediates this process. A systemic reaction (allergy) to the drug was unlikely because of the absence of fever, arthralgias, and eosinophilia.

All three cases of subacute liver failure occurred in women. A preponderance of adverse effects in women has been seen with such drugs as methyl-dopa, which is associated with positivity for autoantibodies (11), but this effect was not seen in our patients.

Because severe hepatocellular injury can occur with the use of nefazodone, the drug should perhaps be avoided in patients with preexisting liver disease. Routine liver chemistries should be per-

formed before nefazodone therapy begins, and patients should be monitored regularly. We suggest discontinuing nefazodone therapy if abnormal liver enzyme concentrations develop.

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Requests for Reprints: Fredrick L Weber Jr., MD, Liver Unit, Division of Digestive Diseases, University of Cincinnati Medical Center, 231 Bethesda Avenue, ML 595, Cincinnati, OH 45267.

Current Author Addresses: Drs. Aranda-Michel and Weber: Liver Unit, Division of Digestive Diseases, University of Cincinnati Medical Center, 231 Bethesda Avenue, ML 595, Cincinnati, OH 45267.

Drs. Koehler and Bejarano: Department of Pathology, University of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, OH 45267.

Drs. Poulos, Luxon, and Mobin Khan: Division of Gastroenterology and Hepatology, St. Louis University, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110.

Drs. Ee and Balistreri: Division of Pediatric Gastroenterology and Nutrition, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229.

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