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CASE REPORT

Acute Liver Failure After Treatment with Nefazodone

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KEY WORDS: nefazodone; antidepressants; acute liver failure.

Nefazodone, a new serotonergic modulating anti-depressant drug approved for treatment of major depression acts by blocking the postsynaptic 5HT 2A receptor and inhibiting serotonin and noradrenaline uptake. Its side effect profile demonstrates that it has decreased anticholinergic, antihistaminic, αadre no-lytic, and sedative activity relative to traditional anti-depressants (1). Although such agents (2, 3) have been associated with a low incidence of idiosyncratic hepatic injury, we report a patient with acute liver failure associated with nefazodone.

CASE REPORT

A 73ye arld woman was prescribed nefazodone 200 mg twice a day and lorazepam 1.5 mg/day for depression. Forty-nine days later she presented with a twowe ek history of abdominal discomfort, anorexia, vomiting, and dark urine. She had a history of alcohol use (<40 g/week) and smoked 50 packs/year. She denied the use of any other drugs or herbal remedies. Nefazodone was discontinued. Physical examination revealed jaundice and abdominal tenderness. Aspartate aminotransferase activity was 1318 units/liter, alanine aminotransferase 834 units/liter, alkaline phosphatase 115 units/liter, and γ-glutamyl transferase 250 units/liter; total bilirubin was 292.4 μmol/liter (with a direct bilirubin level of 278.7 μmol/liter) and prothrombin time of 15 sec. Blood levels of acetaminophen and drugs of abuse were negative.

Ultrasonographic examination revealed a normal liver; gallstones were seen but not expanded bile ducts. A shadow in the distal common duct suggested cholelithiasis. During exploratory laparotomy three days later, the gallbladder was removed and subsequent common duct exploration revealed no lithiasis. Intraoperative liver biopsy showed diffuse hepatocellular necrosis, more prominent in zone 3 with a moderate inflammatory infiltrate (mainly lymphocytes and some eosinophils). Ballooning of hepatocytes and acido philic bodies was also seen. There was some degree of parenchymal collapse. Bile ducts were normal. Mild macrovesicular steatosis was present (Figure 1).

The patient’s level of consciousness deteriorated. A computed tomography scan of the brain ruled out ischemic lesions or intracranial hemorrhage. An electroencephalogram showed no focal damage. There were no apparent risk factors for infectious hepatitis, and she had no recent history of blood transfusion or sexual contact. Serological studies ruled out viral hepatitis A, B, and C (the latter by polymerase chain reaction), cytomegalovirus, herpes simplex and Epstein-Barr virus infection. Serum antitissue antibodies were all negative except for moderately raised titers of antismooth muscle antibodies (1/80). An abdominal Doppler ultrasonographic examination ruled out supraventricular vein thrombosis.

Total bilirubin rose to 499.3 μmol/liter, grade III encephalopathy persisted, with a prothrombin time of 20 sec, and the patient died 28 days after admission.

DISCUSSION

Drugs are a frequently unrecognized cause of many unexplained cases of acute liver failure (4). The cause of hepatic failure in such cases is impossible to determine with complete reliability since there is no information regarding withdrawal and rechallenge. Nevertheless, the clinical course, laboratory data, and biopsy findings in our patient were most consistent with acute hepatic failure related to nefazodone. Other possible causes were ruled out. Although the patient had a history of mild alcohol use and there was some degree of hepatic steatosis, neither the histological picture nor the biochemical liver profile were consistent with alcoholic hepatitis. Acetaminophen hepatotoxicity, as a therapeutic misadventure, in the setting of alcohol use could also be excluded. Moreover, there is no published evidence of interaction between nefazodone and lorazepam resulting in

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increased risk of liver injury (1). The absence of hypersensitivity symptoms and the delayed onset of injury suggest that a toxic metabolite may be responsible.

Idiosyncratic metabolic reactions are often associated with partial dose dependence and a relationship to drug metabolism (5). Nefazodone is extensively biotransformed in the liver, exhibits nonlinear pharmacokinetics, and has reduced hepatic clearance in the elderly (6). Metabolism of the mebrofoline neryl-piperazine moiety, a metabolite common to nefazodone and trazodone, is mediated by CYP2D6, which shows genetic polymorphism (7). Therefore, substantially higher steadystate plasma concentrations are reached in poor metabolizers. Trazodone, to which is structurally related to nefazodone, has been reported to cause hepatotoxicity (8).

In controlled clinical trials nefazodone has been found to be safe and well tolerated with no evidence of specific organ toxicity (9). In contrast to this experience in clinical trials, the WHO International Collaborative Drug Monitoring Programme had received 90 reports of liver disorders (from a total of 2686 reports of adverse reactions to nefazodone), one of which reported fatal acute liver failure in a 80-year-old man who was taking nefazodone 50 mg/day. Of note, the data sheet for nefazodone makes no mention of possible adverse hepatic effects. In conclusion, clinicians should be aware of the potential hepatotoxicity of nefazodone, and we believe that in elderly patients, especially women, a reduced dose should be encouraged.

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