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Single Case

Lorazepam as a Cause of Drug-Induced Liver Injury

Toshio Arai[a] Kazutoyo Kogi[a] Yuki Honda[b] Takao Suzuki[c]
Koji Kawai[d] Masako Okamoto[a] Takahiro Fujioka[e] Nobuhiro Murata[a]

[a]Department of Internal Medicine, Uenohara Municipal Hospital, Uenohara-shi, Japan; [b]Department of Diagnostic and Generalist Medicine, Dokkyo Medical University Hospital, Tochigi, Japan; [c]Internal Medicine and Gastroenterology, Kusabana Clinic, Tokyo, Japan; [d]Department of Gastroenterology, Ito Municipal Hospital, Shizuoka, Japan; [e]Department of Gastroenterology and Hepatology, Nerima-Hikarigaoka Hospital, Tokyo, Japan

Keywords
Lorazepam · Depression · Drug-induced liver injury

Abstract
Lorazepam is a benzodiazepine derivative that is globally used for the therapy of anxiety and insomnia. A 51-year-old Japanese man with yellowish discoloration of the eyes and skin and pruritus was admitted due to liver dysfunction. He had taken lorazepam approximately 5 months prior to this admission. The clinical presentation and pathologic findings in the liver were consistent with drug-induced liver injury. After cessation of lorazepam, treatment with Stronger neo-minophagen C and ursodeoxycholic acid was started, and his liver injury resolved after 59 days. This case must serve as a warning to physicians to be aware of the possibility of unexpected liver injury caused by lorazepam.

Background

Lorazepam, which is a 3-hydroxy benzodiazepine derivative that is used as therapy for anxiety and insomnia [1], has increased in popularity not only in the United States but also in Asia [1]. This drug is absorbed by the gastrointestinal tract after oral administration. After

KARGER

Toshio Arai, MD, PhD
Department of Internal Medicine, Uenohara Municipal Hospital
3504-3, Uenohara
Uenohara-shi, Yamanashi 409-0112 (Japan)
E-Mail toshio-a@ever.ocn.ne.jp

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administration, it quickly distributes to the brain and binds to the gamma-aminobutyric acid (GABA) receptor to enhance GABA-mediated inhibition of synaptic transmission in the several regions of the central nerve system, resulting in anxiolytic and hypnotic properties [1–3]. The major metabolic pathway of this drug involves binding to glucuronic acid at 3 positions, followed by urinary excretion of the inactive glucuronide metabolite. Lorazepam is known to have prolonged elimination half-life and increased volume of distribution in elderly patients or those with kidney dysfunction, but its kinetics is only influenced minimally by the liver [1–3]. The common side effects of lorazepam are amnesia, drowsiness, lethargy, and fatigue [1, 2, 4]. Here we reported an extremely rare case of lorazepam drug-induced liver injury (DILI), which, to the best of our knowledge, has not been previously reported.

Case Report

A 51-year-old Japanese man presented with yellowish discoloration of the eyes and skin and pruritus. Since he was 44 years old, he had been treated for depression with lorazepam, in addition to duloxetine, brotizolam, promethazine, etizolam, and sulpiride. He denied excessive alcohol use; indeed his alcohol consumption was less than 30 g/day. He had no other significant past medical history. Prior to this admission, he had been medicated with lorazepam for approximately 5 months and with the other drugs for 9 months.

On admission, he had stable vital signs. Physical examination showed only generalized jaundice. The cardiovascular and respiratory examinations were normal. The abdomen was nondistended, had normal bowel sounds, had no tenderness in the right upper quadrant, and had no signs of hepatosplenomegaly and peritonitis. His complete blood count was within normal limits. His other laboratory data showed extremely elevated total bilirubin at 26.8 mg/dL (upper limit of normal [ULN], 1.2 mg/dL); direct bilirubin at 20.8 mg/dL (ULN, 0.4 mg/dL); aspartate aminotransferase at 250 IU/L (ULN, 33 IU/L); alanine aminotransferase at 99 IU/L (ULN, 37 IU/L); alkaline phosphatase at 974 IU/L (ULN, 338 IU/L); and albumin at 2.4 mg/dL (lower limit of normal, 3.8 mg/dL). Extensive workup was negative for other causes of liver injury, including viral hepatitis A, B, and C. Epstein-Barr virus and cytomegalovirus serologies; antinuclear antibodies, smooth muscle antibodies, and antimitochondrial antibodies; ceruloplasmin; and iron studies were likewise negative. Magnetic cholangiopancreatography was normal and showed nondilated common bile duct.

Cholestasis-type DILI secondary to lorazepam was suspected, based on a score of 8 or "high possibility" on the 2004 diagnostic criteria of the Digestive Disease Week Japan (DDW-J) [5]. Liver biopsy on day 13 showed intrahepatocellular cholestasis, lymphocytic infiltrates, neutrophils, eosinophils, and rare necrotic hepatocytes (Fig. 1), all of which were consistent with DILI [6, 7]. Lorazepam and the other drugs were discontinued, and his liver enzymes normalized after treatment with Stronger neo-minophagen C 60 mL/day for 8 days and ursodeoxycholic acid 600 mg/day for 13 days (Fig. 2). On the 59th day of follow-up, his liver enzymes had further decreased in trend, with resolution of jaundice and pruritus. Moreover, there was no recurrence of depression after drug cessation.

Discussion

Lorazepam is a kind of benzodiazepine, which is widely used in psychiatric therapy and is metabolized by cytochrome P450 enzymes, conjugated with glucuronide, and excreted

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almost entirely in the urine [1–3]. Lorazepam does not produce active metabolites [1–3]. A recently developed open access website, called the Liver Tox (http://livertox.nih.gov) [8], has not reported a case of lorazepam causing liver injury. One epidemiological study suggested that certain pretreated physiochemical properties of certain classes of drugs could increase the risk of DILI, although the data regarding this issue are equivocal [9]. The published pharmacokinetics of lorazepam stated that it is not substantially metabolized by the liver but is mainly eliminated by glomerular filtration [2]. Therefore, there are currently no suggested dose adjustments for lorazepam in patients with liver disease. In this case, we assumed that immune-mediated effects might also have been involved.

There might be an underexplored association between hepatocellular dysfunction and lorazepam in the setting of chronic alcoholic liver disease, which, in itself, has a potential increased risk for DILI [9–11]. This patient in this study showed a delayed presentation of lorazepam DILI, whereas those in the previous clinical case reports on several antidepressant agents, such as paroxetine, nefazodone, and duloxetine, showed both acute and delayed presentations of DILI [12, 13]. In this case, the other potential etiologies, such as viral hepatitis, autoimmune hepatitis, Wilson's disease, and hemochromatosis, were ruled out, and the imaging modalities, including ultrasound, CT, and magnetic cholangiopancreatography, were negative. Only lorazepam was positive for drug-induced stimulation test. Correlating these results with the Japanese DDW-J clinical diagnostic criteria for DILI, lorazepam was the most likely etiology of this patient's DILI.

This patient did not develop recurrence of depression after drug cessation. There was one similar case report on a patient who recovered from depression after the DILI [14]. It was assumed that the high fever caused by the DILI might be involved in this phenomenon. Nonetheless, the severity of DILI may be minimized by prompt recognition and early withdrawal of the agent. Future cases of suspected lorazepam-induced hepatotoxicity should be reported and efforts to delineate the mechanism of injury should be undertaken.

Statement on Ethics

There are no ethical conflicts to declare.

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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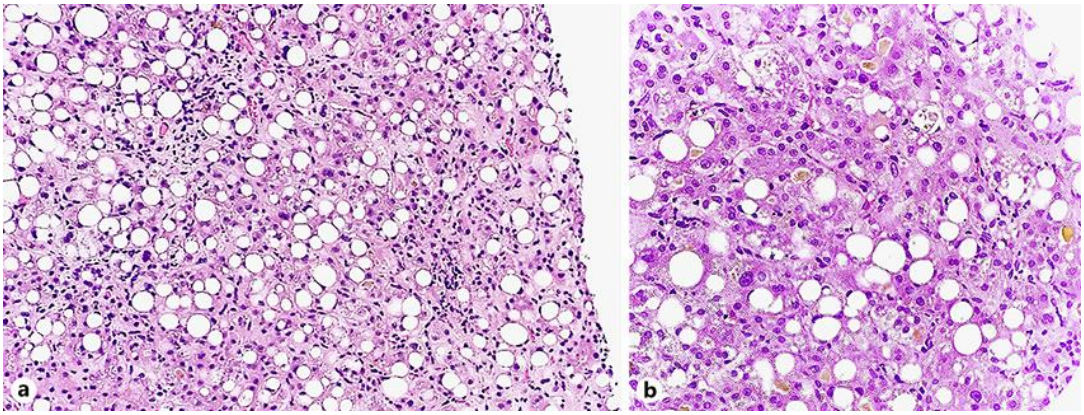

Fig. 1. Photomicrographs of the liver biopsy specimens. **a** There is hepatic macrovesicular steatosis (hematoxylin and eosin staining, ×20). **b** There are mixed inflammatory infiltrates that comprise lymphocytes, neutrophils, and bile plug formations in bile capillaries; there are also numerous fat vacuoles (hematoxylin and eosin staining, ×40).

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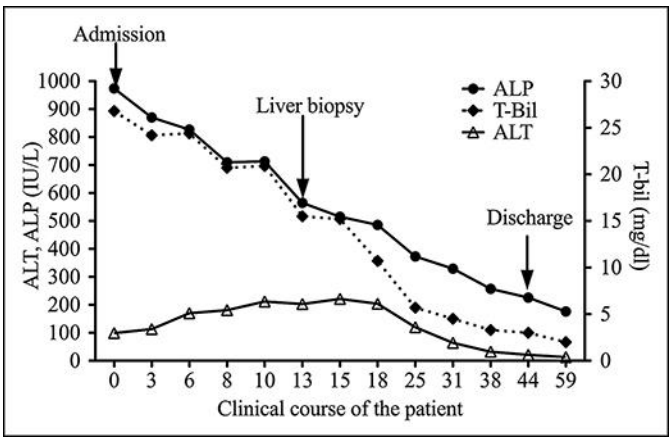

Fig. 2. Time course of liver function tests. Total bilirubin (T-bil), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels are shown by the dotted line, black line, and bold line, respectively. Approximately 2 months after discontinuing lorazepam, the total bilirubin, alanine aminotransferase, and alkaline phosphatase levels normalized.