Voriconazole-Induced Hepatotoxicity Presenting With Severe Hepatic Encephalopathy After Liver Transplantation

Syed Haris Tasleem, MD¹, and Mitchell S. Cappell, MD, PhD²

¹Division of Multi-Organ Transplantation, William Beaumont Hospital, Royal Oak, MI
²Division of Gastroenterology and Hepatology, William Beaumont Hospital, Royal Oak, MI

ABSTRACT

Voriconazole-induced hepatotoxicity is a relatively rare but serious clinicopathologic entity. This drug is frequently used for invasive aspergillosis and other fungal infections. We report a patient with alcoholic cirrhosis who developed hepatic encephalopathy due to voriconazole administered for invasive pulmonary aspergillosis and subsequently showed marked improvement in mental status with dose adjustment of the drug. The patient eventually underwent an uneventful liver transplant. Histopathologic examination of the diseased liver specimen revealed numerous rhomboid-shaped crystals, deemed secondary to liver injury after voriconazole-induced hepatotoxicity. Additionally, this article briefly reviews the available data on voriconazole-induced hepatotoxicity with special emphasis on plasma drug concentration monitoring.

INTRODUCTION

Patients with chronic liver disease are particularly prone to develop invasive pulmonary aspergillosis, which requires early diagnosis and aggressive therapy.¹ ² Voriconazole is the primary therapy for invasive aspergillosis, especially in immunocompromised patients. Elimination of voriconazole depends entirely on the hepatic cytochrome P450 system.³ Patients with cirrhosis have an increased risk of hepatotoxicity due to abnormal hepatic metabolism of this drug. However, data on the appropriate dosage and safety of voriconazole in patients with severe liver disease are scarce.⁴ We report a patient with cirrhosis who developed voriconazole-related hepatic encephalopathy that subsequently improved with dose adjustment of the drug. Furthermore, biopsy of the explant revealed unusual chemical depositions due to voriconazole-induced hepatotoxicity.

CASE REPORT

A 51-year-old white man with a history of Crohn’s disease status post–right hemicolectomy 15 years ago and alcoholic cirrhosis presented with progressive jaundice for 4 weeks. His Crohn’s disease was now in remission, and he stopped drinking 7 months ago. At presentation, he was hemodynamically stable. Physical examination revealed jaundice, ascites, and splenomegaly. Laboratory studies showed the following: aspartate aminotransferase 88 U/L, alanine aminotransferase (ALT) 58 U/L, alkaline phosphatase 106 U/L, total bilirubin 30.8 mg/dL, direct bilirubin 18.2 mg/dL, serum albumin 2.4 g/dL, and international normalized ratio 2.2. The patient had a Model End-Stage Liver Disease (MELD) score of 41, consistent with advanced decompensated liver disease. After evaluation, he was placed on the liver transplant waiting list. However, on day 5 of admission, he developed dyspnea and non-productive cough. His temperature was 36.3°C, respiratory rate 20 per minute, and oxygen saturation 92% on room air. Chest computed tomography (CT) revealed abnormal patchy interstitial alveolar airspace disease with bilateral mid-upper lobe predominance and small pleural effusions (Figure 1). Subsequently, he was diagnosed with invasive pulmonary aspergillosis based on the standard set of investigations.
Treatment was initiated with oral voriconazole (Vfend; Pfizer, New York, NY) 400 mg twice daily for 1 day and maintained at 150 mg twice daily thereafter. The patient was discharged from the hospital on day 13 in stable condition on maintenance therapy. After 10 days, he was readmitted with progressive confusion and stupor. Head CT showed no abnormalities. Laboratory studies revealed the following: serum ammonia 194 μmol/L, ALT 35 U/L, alkaline phosphatase 94 U/L, total bilirubin 21.4 mg/dL, direct bilirubin 20.8 mg/dL, albumin 3.5 g/dL, and international normalized ratio 2.1. The MELD score was 37. He denied use of any other medications. The serum voriconazole trough level was highly supratherapeutic at 13 μg/mL. Voriconazole was considered the likely cause of his hepatic encephalopathy, and it was discontinued. Mental status of the patient gradually improved. After 8 days, the therapy was restarted at a reduced dose of 175 mg/d. He then tolerated the adjusted dose without further supratherapeutic levels (Figure 2). On day 15, he was discharged from the second hospitalization.

The patient underwent uneventful deceased donor liver transplant 18 days after hospital discharge. Biopsy of the native liver specimen revealed severe hepatocellular degeneration associated with cholestasis and marked hepatic cholangial/ductular proliferation with cirrhosis, suggestive of acute/subacute liver injury. Furthermore, deep amber-yellow crystals were present intracellularly, which stained bright golden yellow under polarized light (Figure 3). These crystalline depositions were also clearly noted in extracellular locations (Figure 4). At the 6-month follow-up, chest CT without contrast revealed resolution of patchy interstitial alveolar airspace disease and significant improvement of pleural effusions relative to the previous examination (Figure 5). The patient continued to do well with well-preserved liver function.

**DISCUSSION**

We present a case of severe voriconazole-induced hepatotoxicity in a patient with alcoholic cirrhosis that was associated with (i) highly elevated (toxic) serum voriconazole levels; (ii) reversal of hepatotoxicity after voriconazole cessation; (iii) and findings suggestive of foreign crystals, presumably of voriconazole, on the removed liver after liver transplantation, despite administration of standard drug dosages.

Although voriconazole-induced hepatotoxicity has been reported previously, the exact mechanism and direct cause-effect relationship remains to be established. The plasma level of this drug...
is the best predictor of its efficacy and toxicity.\textsuperscript{5,6} A serum voriconazole concentration of 0.5 mg/L was reasonably efficacious, and a trough concentration of \textgreater{}3.0 mg/L was considered hepatotoxic.\textsuperscript{7} However, a major dilemma associated with voriconazole is the large steady-state concentration variability. For example, in 1 study of 69 patients, voriconazole steady-state concentrations ranged from 0 to 16.6 μg/mL, despite administering the standard dose.\textsuperscript{8} Furthermore, this range was even wider (<0.10–20 mg/L) in another study.\textsuperscript{9} Several factors contribute to this phenomenon, including nonlinear drug pharmacokinetics, patient age, sex, weight, liver disease, and genetic polymorphism in the CYP2C19. As voriconazole is mainly metabolized in the liver, hepatic failure leads to high plasma levels.\textsuperscript{10} In the current patient, the serum voriconazole level was 13 μg/mL at a dose of 300 mg/d, but he had chronic liver disease and consequently developed hepatic encephalopathy.

No consensus exists on the drug plasma concentration for voriconazole, and data on safety of this medication are controversial in patients with severe chronic liver disease. It is notable that the toxicity predominantly occurs with higher doses and can be interrupted by prompt dose reduction. However, plasma concentrations are fairly unpredictable even in an individual patient receiving this medication at different occasions.\textsuperscript{11} In addition, voriconazole drug monitoring in patients with or without liver disease might not be predictive of hepatotoxicity, and liver function monitoring was considered superior in this regard.\textsuperscript{12} Liu et al demonstrated that the plasma trough concentration of voriconazole can be used to predict drug efficacy and toxicity in patients with chronic liver disease.\textsuperscript{13} They reported a case of voriconazole plasma concentration of 8.1 μg/mL at a dose of 1.78 mg/kg per 12 hours in a patient with subacute liver failure (aspartate aminotransferase 314 U/L; ALT 254 U/L; total bilirubin 389 μmol/L).\textsuperscript{13} They emphasized that dose adjustment in patients with liver toxicity can significantly improve acute liver injury. The present case further validates these findings because our patient showed significant improvement in mental status after the dose was reduced.

Although the mental status improved after drug dose reduction in this patient, histopathologic examination of the explanted liver showed rhomboid-shaped crystals. These crystals were not attributable to alcoholic liver disease, implicating a superimposed additional chemical injury. He did not have a history of any other disease or receiving any other drugs that would cause such crystalline liver depositions. Thus, the patient’s recent treatment with voriconazole for \textit{Aspergillus} lung infection was believed to be the highly likely reason for these crystals and severe acute liver

**Figure 3.** (A) Histopathologic aspect of the explant liver specimen showing voriconazole drug crystals. The hepatocytes show the intracellular presence of some light brown pigmentation, compatible with bile stasis (hematoxylin & eosin [H&E]; 600×). (B) Bright golden yellow voriconazole crystals under polarized light (600×). H&E staining of the liver specimen showing deep amber-yellow extracellular crystalline structures, some of which have a rhomboid configuration. The hepatocytes show the intracellular presence of some light brown pigmentation, compatible with bile stasis (600×).

**Figure 4.** (A) Histopathologic aspect of the explant liver specimen showing both intracellular and extracellular, deep amber-yellow crystalline structures, which represent the voriconazole drug crystals. The hepatocytes show intracellular presence of some yellow to light brown pigmentation, compatible with bile stasis (hematoxylin & eosin; 600×). (B) Voriconazole crystals showing bright golden yellow appearance under polarized light (600×).
injury. In the literature, periostitis and fluorosis secondary to voriconazole are well-established adverse events. However, to our knowledge, liver deposition of voriconazole with histopathologic evidence of crystals of this implicated drug is rare. Hence, further research is warranted to investigate the safety of voriconazole in liver failure patients.

**DISCLOSURES**

Author contributions: S.H. Tasleem designed the study, reviewed the literature, drafted the manuscript, and is the article guarantor. M.S. Cappell reviewed the manuscript and revised it for important intellectual content.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received June 5, 2018; Accepted November 12, 2018

**REFERENCES**

1. Bajaj JS, Rajender Reddy K, Tandon P, et al. Prediction of fungal infection development and their impact on survival using the NACSELD Cohort. *Am J Gastroenterol*. 2018;113(4):556–63.
2. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327–60.
3. Zonios D, Yamazaki H, Murayama N, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis*. 2014;209(12):1941–8.
4. Levine MT, Chandrasekar PH. Adverse effects of voriconazole: Over a decade of use. *Clin Transpl*. 2016;30(11):1377–86.
5. Solis-Munoz P, Lopez JC, Bernal W, et al. Voriconazole hepatotoxicity in severe liver dysfunction. *J Infect*. 2013;66(1):80–6.
6. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R. Voriconazole therapeutic drug monitoring: Focus on safety. *Expert Opin Drug Saf*. 2010;9(1):125–37.
7. Jin H, Wang T, Falcone BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: A systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71(7):1772–85.
8. Saini L, Seki JT, Kumar D, et al. Serum voriconazole level variability in patients with hematological malignancies receiving voriconazole therapy. *Can J Infect Dis Med Microbiol*. 2014;25(5):271–6.
9. Chu HY, Jain R, Xie H, Pottinger P, Fredricks DN. Voriconazole therapeutic drug monitoring: Retrospective cohort study of the relationship to clinical outcomes and adverse events. *BMC Infect Dis*. 2013;13:105.
10. Zhang S, Pillai VC, Mada SR, Strom S, Venkataramanan R. Effect of voriconazole and other azole antifungal agents on CYP3A activity and metabolism of tacrolimus in human liver microsomes. *Xenobiotica*. 2012;42(5):409–16.
11. Trifilio SM, Yarnold PR, Scheetz MH, PI J, Pennick G, Mehta J. Serial plasma voriconazole concentrations after allogeneic hematopoietic stem cell transplantation. *Antimicrob Agents Chemother*. 2009;53(5):1793–6.
12. Lutsar I, Hodges MR, Tomaszewski K, Troke PF, Wood ND. Safety of voriconazole and dose individualization. *Clin Infect Dis*. 2003;36(8):1087–8.
13. Liu X, Su H, Tong J, et al. Significance of monitoring plasma concentration of voriconazole in a patient with liver failure: A case report. *Medicine (Baltimore)*. 2017;96(42):e8039.

*Copyright: © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.*