Short Communication

Voriconazole-Induced Hepatitis via Simvastatin- and Lansoprazole-Mediated Drug Interactions: A Case Report and Review of the Literature

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ABSTRACT
Therapeutic voriconazole concentrations have a narrow window of effectiveness before causing cholestatic hepatitis. After undergoing 1 year of voriconazole therapy for pulmonary aspergillosis, a 44-year-old man began treatment with 30 mg lansoprazole for gastroesophageal reflux symptoms. Within 5 days of starting treatment with lansoprazole, the patient presented with fatigue, jaundice, and cholestatic hepatitis. The hepatitis promptly resolved after stopping lansoprazole treatment. Sixteen months later, the patient was given simvastatin therapy, as recommended by the American Diabetes Association to prevent cardiovascular disease for patients with diabetes who are aged >40 years and have one additional risk factor. Within 2 weeks of taking simvastatin, a 3-hydroxy-3-methylglutaryl CoA reductase (statin) therapy, the patient redeveloped fatigue, jaundice, and cholestatic hepatitis. He described both episodes of fatigue and jaundice similarly in terms of onset and intensity. Voriconazole is metabolized by both CYP2C19 and CYP3A4 isoenzymes. Lansoprazole is an inhibitor of the CYP2C19 isoenzyme. Competition between voriconazole and lansoprazole likely led to increased voriconazole serum concentration and acute cholestatic hepatitis in this patient. Simvastatin inhibits the CYP3A4 isoenzyme. After the patient took 10 mg simvastatin daily for 2 weeks, cholestatic hepatitis occurred. The voriconazole concentration remained elevated (4.1 μg/ml) when measured 15 days after stopping simvastatin. The patient’s Naranjo Adverse Drug Reaction Probability Scale score of 7 revealed that the cholestatic hepatitis was probably precipitated by lansoprazole. Likewise, the patient’s Naranjo score of 9 also revealed that cholestatic hepatitis was attributable to a definite adverse drug reaction precipitated by the addition of simvastatin to the stable baseline regimen of voriconazole. In a single patient, two different inhibitors of the cytochrome P450 pathway stimulated voriconazole-induced cholestatic hepatitis. Although the major cytochrome P450 pathways for the metabolism and clearance of lansoprazole and simvastatin are different, they both likely contributed to the reduced hepatic clearance of voriconazole in this patient.

Introduction
Voriconazole, a second-generation synthetic derivative of flucona- zole, was approved by the U.S. Food and Drug Administration in May 2002 for the treatment of invasive aspergillosis. Voriconazole is metabolized by cytochrome P450 isoenzymes CYP2C19 and CYP3A4. Voriconazole has the potential for its metabolism to be affected by and affect the metabolism of other drugs and cause hepatitis. There is a near-linear dose-response relationship with serum bilirubin concentration and voriconazole concentrations; the higher the concentration of voriconazole, the higher the risk for cholestatic hepatitis (Tan et al., 2006). Cholestatic hepatitis is not an uncommon finding in patients treated with voriconazole (Tan et al., 2006). Here, we report a case of recurrent cholestatic hepatitis in a patient taking voriconazole induced initially by concomitant use of lansoprazole and later by concomitant use of simvastatin.

Case Report
Clinical and laboratory data were obtained with the patient’s consent. The patient’s primary care provider advised him to start a statin medication for treatment of his low-density lipoprotein cholesterol, which at the time was above normal.

The patient, a 44-year-old Caucasian man with a history of Wegener’s granulomatosis and pulmonary aspergillosis complicated by corticosteroid-induced diabetes and unknown CYP2C19 genotype, had been taking voriconazole (200 mg twice a day) for 1 year for treatment of aspergillosis. In addition, the patient was taking prednisone and cyclophosphamide for Wegener’s granulomatosis, trimethoprim-sulfamethoxazole for Pneumocystis carinii (now referred to as Pneumocystis jiroveci) pneumonia prophylaxis, and insulin for diabetes. Approximately 10 days before hospital admission, the patient was directed to take lansoprazole 30 mg daily for treatment of epigastric discomfort. He was diagnosed with gastrointestinal reflux disease based on clinical symptoms. His epigastric discomfort had been present daily for approximately 1 month and there was no relief with nonprescription remedies. The patient’s epigastric pain was improved while he was taking lansoprazole, but he presented to our hospital with complaints of painless jaundice and fatigue.

Liver function test (LFT) results revealed cholestatic hepatitis, with a serum aspartate aminotransferase level of 264 mU/ml (reference, 15–41 mU/ml), an alanine aminotransferase level of 362 mU/ml (reference, 17–63 mU/ml), an alkaline phosphatase level of 406 mU/

ABBRÉVOLUTION: LFT, liver function test.
ml (reference, 38–126 mU/ml), a total bilirubin level of 14 mg/dl (reference, 0.2–1.2 mg/dl), and a direct bilirubin level of 10 mg/dl (reference 0.1–0.3 mg/dl) (Fig. 1). These tests had been normal 1 month earlier. Serologic tests were negative for hepatitis A, B, and C viruses. Results from biliary ultrasonography and abdominal computed tomography demonstrated intrahepatic ductal dilatation without obstruction.

Lansoprazole and voriconazole therapy was discontinued and LFT results returned to normal within 4 weeks. Voriconazole was reintroduced at 200 mg twice a day to continue treatment of invasive aspergillosis upon normalization of LFT results, with serial computed tomography monitoring for progression of disease. LFT results remained normal for the next 16 months.

After 16 months, the patient was started on simvastatin 10 mg daily for hyperlipidemia. This drug was started based on the indication for 3-hydroxy-3-methylglutaryl CoA reductase therapy in patients with diabetes to obtain a low-density lipoprotein cholesterol concentration < 100 mg/dl. Within 2 weeks, the patient developed nausea, malaise, and severe jaundice. After 3 weeks of treatment with both simvastatin and voriconazole, the patient self-discontinued both drugs. The patient’s serum voriconazole concentration obtained 15 days after the cessation of simvastatin was in the therapeutic range of 4.1 μg/ml measured by high pressure liquid chromatography upon admission. The patient’s serum level while taking simvastatin was not obtained directly but was calculated to be twice the therapeutic concentration as a result of the competition of clearance with simvastatin via the CYP3A4 enzyme system. The patient was hospitalized for recurrent cholestatic hepatitis (aspartate aminotransferase, 823 mU/ml; alanine aminotransferase, 893 mU/ml; alkaline phosphatase, 789 mU/ml; total bilirubin, 15.4 mg/dl; and direct bilirubin, 11.3 mg/dl). Results of repeated serologic tests were again negative for hepatitis A, B, and C.

A right upper quadrant abdominal ultrasound showed a small dilated intrahepatic duct. The LFT values peaked 2 days before admission (13 days after stopping simvastatin) and slowly resolved as voriconazole was temporarily discontinued. LFT results normalized within 1 month. Seven months after the episode of hepatitis, while taking the same dose of voriconazole and other medications except for simvastatin, the patient’s serum voriconazole concentration was 2.9 μg/ml and the LFT panel results remained normal. The patient has not had any recurrent fatigue or jaundice.

The patient’s Naranjo Adverse Drug Reaction Probability Scale score of 7 revealed that his cholestatic hepatitis was probably precipitated by lansoprazole. The Naranjo nomogram is a 10-point questionnaire for determining the likelihood of whether an adverse drug reaction is actually due to the drug, rather than the result of other factors, in which terms such as definite (>8 points), probably (4–8 points), possible (1–4 points), and doubtful (0 points) are calculated (Naranjo et al., 1981). Likewise, the patient’s Naranjo scale score of 9 revealed that cholestatic hepatitis was definitely precipitated by the addition of simvastatin to the stable baseline regimen of voriconazole.

**Discussion**

CYP2C19 is the major isoenzyme involved in voriconazole metabolism, although CYP3A4 and CYP2C9 also contribute (Groll et al., 2003). There is wide variability in the rate of voriconazole metabolism observed between subjects, partially because of the genetic differences found among patients. CYP2C19 exhibits genetic polymorphism in the population, resulting in different degrees of metabolism of substrates. For example, 20% of Asians and 5% of Caucasians have CYP2C19 alleles that result in them being poor metabolizers (Manzi and Shannon, 2005). Therefore, the individual patient’s susceptibility to drug-induced hepatitis during the chronic use of voriconazole may be attributable to the genetic differences in these isoenzymes, which contribute to the overall metabolism of multiple drugs.

CYP2C19 is also the major isoenzyme that metabolizes the drug lansoprazole, with some additional metabolism by CYP3A4 (Naritomi et al., 2004). In addition, lansoprazole is a potent inhibitor of CYP2C19 in vitro (Li et al., 2004); therefore, lansoprazole may have reduced the hepatic clearance of voriconazole in our patient, leading to drug-induced hepatitis. In vivo data suggest that this increase in voriconazole concentration may only occur in patients who are poor metabolizers of CYP2C19 (Iagaki et al., 2004). However, a recent report showed no association with poor metabolizers of CYP2C19, CYP3A5, or CYP2C9 (Levin et al., 2007). A study by Tsubokura et al. (2010) showed that a patient taking voriconazole developed a fatal arrhythmia, owing to the prolongation of the QT interval when the patient was also given lansoprazole; the combination of the two drugs resulted in an increased voriconazole concentration.

Simvastatin is a CYP3A4 substrate whose plasma concentration can increase 20-fold when given to patients who are also taking itraconazole (Neuvonen et al., 1998). Likewise, voriconazole
concentration would increase with concomitant voriconazole administration, which was observed 15 days after our patient stopped taking simvastatin. The serum voriconazole concentration should decrease based on the known metabolism of both medications. However, based on the development of drug-induced cholestatic hepatitis, simvastatin most likely increased voriconazole concentration. It was previously reported that incidences of voriconazole-induced LFT abnormalities are directly related to the plasma voriconazole concentration (Tan et al., 2006). Furthermore, simvastatin-induced hepatitis is rare (5 of 1188 cases of drug-induced liver injury; Russo et al., 2014), simvastatin-induced cholestatic hepatitis has only been reported in two previous case reports (Ballaré et al., 1991; Lata and Chudy, 2006), and three of the five recently reported patients (Russo et al., 2014). Therefore, we conclude that it is unlikely that simvastatin alone was responsible for our patient’s cholestatic hepatitis.

A plasma voriconazole concentration of 4.1 μg/ml, which was obtained for this patient after he had stopped simvastatin for a 15-day period, results in abnormal LFT results for approximately 5% of the patient population (Tan et al., 2006). However, this patient’s voriconazole concentration was likely ≥10 μg/ml before he had stopped simvastatin.

It has been reported that there is a near-linear dose-response relationship with serum bilirubin concentration and voriconazole concentration; the higher the concentration of voriconazole, the higher the bilirubin (Tan et al., 2006). The patient’s follow-up voriconazole concentration on the same dose of voriconazole was 2.9 μg/ml without exposure to either CYP3A4 or CYP2C19 medications. LFT results were normal at that time.

Conclusions
Two episodes of cholestatic hepatitis were observed with nearly identical clinical symptoms precipitated by the addition of a single medication to the already prescribed voriconazole, 16 months apart. The similar clinical presentation and two different cytochrome P450 pathways of voriconazole metabolism (CYP2C19 and CYP3A4) suggest that all patient medications must be meticulously monitored to prevent adverse drug–drug interactions. The use of either proton pump inhibitors or 3-hydroxy-3-methylglutaryl CoA reductase inhibitors must be done with the utmost caution in patients receiving antifungal therapy.

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