Voriconazole-Induced Hepatitis via Simvastatin- and Lansoprazole-mediated drug interactions; Case Report and Review of the Literature.

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Running Title: Voriconazole-Induced Hepatitis via 3A4 or 2C19 Inhibition

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Abstract:
Introduction: Therapeutic voriconazole concentrations have a narrow window of effectiveness before causing cholestatic hepatitis. Case presentation: After one year of voriconazole therapy for pulmonary aspergillosis, a 44-year-old male began 30 mg of lansoprazole for gastroesophageal reflux (GERD) symptoms. Within five 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 for diabetic patients over the age of 40 with one additional risk factor to prevent cardiovascular disease. Within 2-weeks of taking simvastatin a HMG CoA reductase (statin) therapy the patients redeveloped fatigue, jaundice and cholestatic hepatitis. The patient described both episodes of fatigue and jaundice similarly in onset and intensity. Conclusion: Voriconazole is metabolized by both cytochrome P450 2C19 and 3A4 isoenzymes. Lansoprazole is an inhibitor of 2C19 isoenzyme. Likely competition between voriconazole and lansoprazole led to increase voriconazole serum concentration and acute cholestatic hepatitis. Simvastatin inhibits the P450 3A4 isoenzyme. After 10 mg of simvastatin a day for two weeks, cholestatic hepatitis occurred. The voriconazole concentration remained elevated (4.1 ug/ml) when measured 15-days after stopping simvastatin. Use of the Naranjo probability scale revealed that the cholestatic hepatitis was probably precipitated by lansoprazole (score 7). Likewise, the Naranjo probability scale revealed that cholestatic hepatitis was due to a definite (score 9) adverse drug reaction precipitated by the addition of the simvastatin to the stable baseline regimen of voriconazole. In a single patient, two different inhibitors of the P450 pathway stimulated a voriconazole induced cholestatic hepatitis. While the major P450 pathway for the metabolism and clearance of lansoprazole and simvastatin are different, they both likely contributed to the reduced hepatic clearance of voriconazole.
Introduction

Voriconazole, a second-generation synthetic derivative of fluconazole, was approved by the Food and Drug Administration in May 2002 for the treatment of invasive aspergillosis. Given voriconazole is metabolized by CYP450 isoenzymes 2C19 and 3A4, it 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). Cholestatic hepatitis is not an uncommon finding in patients treated with voriconazole (Tan) We report a case of recurrent cholestatic hepatitis while on voriconazole induced initially by concomitant use of lansoprazole and later by concomitant use of simvastatin.

Material and Methods:
Clinical and laboratory data were obtained with the consent of the patient. As the primary care provider for this patient, he was advised to start a statin medication for treatment of his LDL cholesterol which at the time was above normal.

Results: Case Report: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 BID) for 1-year for treatment of aspergillosis. Additionally, the patient was taking prednisone and cyclophosphamide for Wegener’s granulomatosis, trimethoprim-sulfamethoxazole for P. carini (new name P.
jiroveci) pneumonitis prophylaxis, and insulin for diabetes. Approximately 10 days prior to hospital admission, the patient was directed to take lansoprazole 30 mg daily for treatment of epigastric discomfort. The diagnosis was gastro-intestinal reflux disease based on clinical symptoms. His epigastric discomfort had been present daily for approximately one month and there was no relief with non-prescription remedies. His epigastric pain was improved on lansoprazole, but he presented to our hospital with complaints of painless jaundice and fatigue. Liver function tests (LFTs) revealed cholestatic hepatitis with a serum aspartate aminotransferase (AST) level of 264 mU/mL (reference 15-41 mU/mL), an alanine aminotransferase (ALT) level of 362 mU/mL (reference 17-63 mU/mL), an alkaline phosphatase (ALP) level of 406 mU/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). These tests had been normal one month earlier. Serologic tests were negative for hepatitis A, B, and C viruses. Biliary ultrasound and abdominal CT demonstrated intrahepatic ductal dilatation without obstruction.

Lansoprazole and voriconazole therapy were discontinued and LFTs returned to normal within 4 weeks. Voriconazole was reintroduced at 200 mg BID to continue treatment of invasive aspergillosis upon normalization of LFTs, with serial CT monitoring for progression of disease. Liver function tests remained normal for the next 16 months.

After sixteen months, the patient was started on simvastatin 10mg daily for hyperlipidemia. It was started based on the indication for HMG CoA reductase therapy in diabetics to obtain an LDL cholesterol concentration < 100 mg/dl. Within two weeks, the patient developed nausea, malaise, and severe jaundice. After three weeks on both simvastatin and voriconazole, the
patient self-discontinued simvastatin and voriconazole. Serum voriconazole concentration obtained 15 days after the cessation of simvastatin was in the therapeutic range of 4.1 ug/ml measured by HPCL upon admission. The serum level while on simvastatin was not obtained directly but was calculated to be twice the therapeutic concentration due to the competition of clearance with simvastatin via 3A4 P450 enzyme system. The patient was hospitalized for recurrent cholestatic hepatitis (AST, 823 mU/mL; ALT 893 mU/mL, ALP 789 mU/mL, total bilirubin 15.4 mg/dL, and direct bilirubin 11.3 mg/dL). Repeated serologic tests were again negative for hepatitis A, B, and C. Right upper quadrant abdominal ultrasound showed a small dilated intrahepatic duct. The LFT values peaked two days prior to admission (13 days after stopping the simvastatin) and slowly resolved as voriconazole was temporarily discontinued. Liver function tests normalized within 1-month. Seven months after the episode of hepatitis, while on the same dose of voriconazole and other medications except for simvastatin, serum voriconazole concentration was 2.9 ug/ml and the LFT panel remained normal. The patient has not had any recurrent fatigue or jaundice.

Use of the Naranjo probability scale revealed that the cholestatic hepatitis was probably precipitated by lansoprazole (score 7). 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 where terms like definite (>8 points), probably (4-8 points), possible 1-4 points and doubtful (0 points) are calculated (Najanjo). Likewise, the Naranjo probability scale revealed that cholestatic hepatitis was definitely (score 9) precipitated by the addition of the simvastatin to the stable baseline regimen of voriconazole.
Discussion:

The major isoenzyme involved in voriconazole metabolism is CYP2C19, although CYP3A4 and CYP2C9 also contribute (Groll). There is a wide variability of results observed between-subjects in the rate of voriconazole metabolism partially due to 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). Therefore, the individual patients’ susceptibility to drug-induced hepatitis during the chronic use of voriconazole may be due 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). Additionally, lansoprazole is a potent inhibitor of CYP2C19 in vitro (Li), therefore, lansoprazole may have reduced the hepatic clearance of voriconazole in our patient, leading to a drug-induced hepatitis. However, in vivo data suggest that this increase in voriconazole concentration may only occur in patients who are poor metabolizers of CYP2C19 (Itagaki). However a recent report found no association with poor metabolizers of CYP2C19, CYP3A5 or CYP2C9 (Levin). Recently a study found that a patient taking voriconazole developed a fatal arrhythmia due to the prolongation of the QT interval when additionally given lansoprazole. The combination of the two drugs resulted in a raised voriconazole concentration (Tsubokura).
Simvastatin is a CYP3A4 substrate, whose plasma concentration can increase 20-fold when given to patients who are also on itraconazole (Neuvonen). Likewise, voriconazole concentration would increase with concomitant voriconazole administration which was observed 15 days after the cessation of taking simvastatin. 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 has been previously reported that incidences of voriconazole-induced liver function test abnormalities are directly related to the plasma voriconazole concentration (Tan). Furthermore, simvastatin induced hepatitis is rare (5 out of 1188 cases of Drug Induced Liver Injury) is rare (Russo) and simvastatin induced cholestatic hepatitis has only been reported in two previous case reports (Ballare, Lata) and three of the five recently reported (Russo). Therefore, we conclude that it is unlikely that simvastatin alone was responsible for the 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 liver function tests for approximately 5% of the patient population (Tan). However, this patient’s voriconazole concentration was likely at or above 10 μg/ml before he had stopped the simvastatin medications.

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). Follow-up voriconazole concentration on the same dose of
voriconazole was 2.9 ug/ml without exposure to other 3A4 or 2C19 medications. Liver function test measurements were normal at that time.

Conclusion: 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 the two different P450 pathways of voriconazole metabolism (2C19 and 3A4) suggest that all patient medications must be meticulously monitored to prevent adverse drug-drug interactions. The use of either proton pump inhibitors or HMG CoA reductase inhibitors must be done with the utmost caution in patients on anti-fungal therapy.

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JLL drafted the paper and figure. JT finalized the draft report and validated all details of the case report. All authors read and approved the final manuscript.

Competing Interests:
The authors declare that they have no competing interests.
References:


Figure 1 Legend: Temporal relation between initiation of lansoprazole, and subsequent simvastatin, to occurrence of the patient’s clinical symptoms and laboratory alterations suggest
drug interaction induced cholestatic hepatitis. Aspartate aminotransferase (AST); alanine aminotransferase (ALT); alkaline phosphatase (ALP); and total bilirubin).
Hospital admission 5 days after starting lansoprazole

Second Hospital admission 14 days after simvastatin administration

16 Months Later