Voriconazole has recently been reported to elevate trough tacrolimus blood concentrations by 10-fold [2]. Such elevated levels have the potential to induce serious adverse events in patients who are not carefully monitored. The present case documents the consequence of elevated tacrolimus concentrations in a patient who developed multifocal leukoencephalopathy. Daily monitoring of tacrolimus trough blood concentrations was performed to adjust the tacrolimus dosage and prevent a potential repetition of this adverse event. The current recommendation to reduce the daily tacrolimus dose by one-third may not maintain tacrolimus concentrations within the therapeutic range. In addition, the duration of inhibition of tacrolimus metabolism after voriconazole therapy is discontinued is not known. Careful monitoring of tacrolimus concentrations is crucial when voriconazole is coadministered with tacrolimus, especially for outpatients.

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developed hepatotoxicity related to fluconazole but subsequently tolerated voriconazole therapy.

The patient was a 32-year-old Hispanic man with a history of type 1 diabetes mellitus who presented with headache and nuchal rigidity; a cavitary lesion was revealed by a chest radiograph, and analysis of CSF samples obtained by lumbar puncture revealed a lymphocytic pleocytosis. The patient began to receive empirical treatment with fluconazole, 1200 mg iv per day, for possible fungal meningitis, and also an oral regimen of isoniazid 300 mg q.d., rifampin 600 mg q.d., pyrazinamide 1500 mg q.d., and ethambutol 1200 mg q.d., for possible tuberculous meningitis. On the first day of azole treatment, the patient’s serum aminotransferase (ALT) level of 20 mU/mL, an AST concentration of 378 mU/mL, an alkaline phosphatase level of 45 U/L, an aspartate aminotransferase (AST) concentration of 378 mU/mL, and a total bilirubin level of 0.6 mg/dL, an alanine phosphatase level of 45 mU/mL, an anaplastic aminotransferase (ALT) level of 20 mU/mL, and an alanine aminotransferase (ALT) level of 20 mU/mL (figure 1). The patient’s serum alanine transaminase (ALT) level of 967 mU/mL. Because of this increase, on day 32 of azole therapy, treatment with fluconazole was again stopped and voriconazole therapy was reinitiated at a dosage of 300 mg iv q12h (figure 1). Within 2 days, the AST level had increased to 143 mU/mL. No other medications were added to or removed from the regimen from days 30 to 34 of azole therapy. The patient was never hypotensive during the hospitalization. Unfortunately, the patient developed obstructive hydrocephalus while receiving therapy and subsequently suffered multiple bilateral cerebral infarcts involving the frontal, parietal, and occipital lobes, as well as the brainstem. He died on day 35 of azole therapy.

Other medications the patient received during this time included fluoxetine, fludrocortisone, prednisone, famotidine, several doses of intracranial amphotericin B deoxycholate, and intravenous amphotericin B deoxycholate, the last of which was administered at a dosage of 0.7 mg/kg per day from days 17 to 20 of fluconazole treatment.

On the basis of the extreme elevation of the transaminase levels, fluconazole therapy was stopped after 22 days of treatment, and voriconazole therapy was initiated at a dosage of 400 mg iv q12h, for 2 doses, and continued at a dosage of 300 mg iv q12h (figure 1). Both the ALT and AST levels steadily decreased following initiation of voriconazole treatment, and the alkaline phosphatase level normalized. No other medications were discontinued from the drug regimen during this time; several medications were added, including levetiracetam for seizure prophylaxis and, on day 2 of voriconazole therapy (day 24 of azole therapy), amphotericin B lipid complex at a dosage of 10 mg/kg per day iv.

After 8 days of voriconazole treatment (30 days of azole therapy), the AST level had decreased to 43 mU/mL and the ALT level had decreased to 164 mU/mL. Voriconazole therapy was therefore stopped, and the patient was rechallenged with fluconazole therapy at a dosage of 400 mg iv q.d. (figure 1). The patient’s transaminase levels immediately rose again over the next 2 days, to an AST level of 72 mU/mL and an ALT level of 209 mU/mL. Because of this increase, on day 32 of azole therapy, treatment with fluconazole was again stopped and voriconazole therapy was reinitiated at a dosage of 300 mg iv q12h (figure 1). Within 2 days, the AST level had normalized and the ALT level had decreased to 143 mU/mL. No other medications were added to or removed from the regimen from days 30 to 34 of azole therapy. The patient was never hypotensive during the hospitalization. Unfortunately, the patient developed obstructive hydrocephalus while receiving therapy and subsequently suffered multiple bilateral cerebral infarcts involving the frontal, parietal, and occipital lobes, as well as the brainstem. He died on day 35 of azole therapy.

Although fluconazole-induced hepatotoxicity is rare (incidence, < 5%), it is well described [2]. The timing of the decreases in this patient’s transaminase levels correlated exactly with a decrease in the dosage of fluconazole and cessation of fluconazole administration,
whereas rechallenge with fluconazole led to a recurrent increase in his transaminase levels. The only other potentially hepatotoxic agents to which the patient was exposed were isoniazid, rifampin, and pyrazinamide. However, he received these drugs during only the initial 6 days of therapy, and treatment with them was stopped 1 week before the rise in transaminase levels was first noted and 3 weeks before the transaminase levels peaked. Although acetaminophen (650 mg q.d. for 4 days) was administered as premedication for amphotericin B dixycholate therapy (on days 17 to 20 of fluconazole therapy), it is unlikely that such a small dosage could mediate severe hepatotoxicity. Thus, on the basis of the timing of fluconazole administration and the lack of exposure to other hepatotoxic drugs, we think that fluconazole therapy was the likely etiology of this patient’s elevated transaminase levels.

In both instances when voriconazole was substituted for fluconazole, the transaminase levels steadily decreased towards normal. Our experience with this patient therefore provides evidence that fluconazole and voriconazole are not necessarily cross-hepatotoxic, and suggests that voriconazole may be cautiously substituted for fluconazole in the treatment of patients with fluconazole-induced hepatotoxicity who require azole therapy for mycotic infections.

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