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## Liver Failure in a Child Receiving Highly Active Antiretroviral Therapy and Voriconazole

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**We describe a 10-year-old child with vertically transmitted acquired immunodeficiency syndrome who was receiving antiretroviral combination therapy and died of liver failure after beginning voriconazole therapy.**

The therapeutic options available to HIV-infected patients have improved since the introduction of HAART. In particular, protease inhibitors have been developed that are substrates of the cytochrome P450 isoenzymes CYP2C9, CYP3A4, and CYP2C19. In vitro studies have indicated that the novel wide-spectrum triazole antifungal agent voriconazole is also a substrate of these cytochrome P450 isoenzymes [1]. We report what is, to our knowledge, the first case of interaction between protease inhibitors and voriconazole.

**Case report.** We treated a 10-year-old girl with vertically acquired AIDS (Centers for Disease Control and Prevention classification, clinical category 3 [C3]) who was admitted to our clinic with thrush and a severe failure to thrive (weight, 21 kg [2.97 SDs below the mean for the age group]; height, 130 cm [2.12 SDs below the mean for the age group]; weight loss, 3 kg in 4 weeks) [2]. She had been treated from the first year of age with various drug combinations and without any prolonged success. Seven months prior to admission, her therapy was switched to a regimen of amprenavir (22.5 mg/kg b.i.d.), didanosine (120 mg/m<sup>2</sup> b.i.d.), nevirapine (4 mg/kg b.i.d.), and a combination of lopinavir (10 mg/kg b.i.d.) and ritonavir (2.5 mg/kg b.i.d.), which she tolerated well. Her HIV RNA level in plasma decreased from 5.46 to 3.11 log copies/mL for 5 months, prior to the development of resistance to each class of antiretroviral drugs available. Genotypic resistance

was measured by sequencing of the reverse transcriptase gene and the protease gene. Relevant mutations found for the reverse transcriptase gene were: 41L, 44D, 62V, 67N, 74V, 101E, 118I, 181C, 184I, 190A, 210W, 215Y, 219R. Relevant mutations found for the protease gene were: 10F, 20R, 30N, 33F, 36L, 54V, 63P, 84V, 88D, 90M). Her HIV RNA level persisted at ~5 log copies/mL, with a CD4<sup>+</sup> T cell count of 160 cells/mm<sup>3</sup> at the time of admission. The patient's failure to thrive was assumed to result from esophageal candidiasis and inadequate caloric intake as the consequence of painful swallowing. Adenovirus was cultured from the patient's stool specimens; neither diarrhea nor fever was present. She was treated empirically with amphotericin B, administered intravenously for 6 weeks. Concurrent medication consisted of a cotrimoxazole (48 mg/kg b.i.d.) and ranitidine (8 mg/kg b.i.d.). The patient developed moderate renal dysfunction and needed supplementation of electrolytes and bicarbonate, whereas clinical symptoms only slightly improved.

Gastrointestinal endoscopy revealed persistent and severe esophageal candidiasis. Cultures of tissue from a biopsy of the esophagus were positive for *Candida albicans*, which had documented resistance to itraconazole and fluconazole but sensitivity to amphotericin B and voriconazole. Intravenous therapy was changed to liposomal amphotericin B (4 mg/kg) and 5-fluorocytosin (100 mg/kg in 4 doses) for 3 weeks. Because of the lack of any clinical improvement, the antimycotic regimen was changed to oral voriconazole (200 mg b.i.d.), which was used on a compassionate use basis after the informed consent of the patient's parents was given.

One day after the start of voriconazole therapy (day 1), liver enzyme levels had slightly risen (table 1). The patient's liver function deteriorated rapidly within 7 days after the start of voriconazole treatment, and voriconazole therapy was stopped on day 7. The results of serologic testing and PCR blood tests for hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) were negative. A retrospective comparison revealed that, after 2 days, the plasma concentrations of the antiretroviral medication were elevated (lopinavir, 10.4 µg/mL; nevirapine, 7.7 µg/mL; amprenavir, 10.9 µg/mL) compared with the levels during the 6 months prior to admission (lopinavir, 3.9–6.0 µg/mL; nevirapine, 3.5–8.4 µg/mL; amprenavir, 3.5–7.7 µg/mL). The patient had no fever; she was alert and neither showed any neurologic symptoms nor complained about pain. In the presence of progressive liver dysfunction, 5 days after the end of voriconazole therapy, HAART was also stopped; however, irreversible liver failure ensued, followed by hepatic

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**Table 1. Laboratory results for a 10-year-old child with AIDS receiving HAART who died of liver failure following treatment with voriconazole.**

Laboratory study	Normal range	Observed value, by day relative to start of VCN therapy								
		-50	-42	-12	1	7 <sup>a</sup>	9	12 <sup>b</sup>	16	28 <sup>c</sup>
AST, U/L	0–40	53	28	54	127	740	1401	5977	8534	593
ALT, U/L	0–45	28	21	23	53	...	209	553	842	334
γ-GT, U/L	0–40	100	91	80	101	...	314	693	...	...
LDH, U/L	0–220	470	298	390	669	2083	3366	8110	10154	...
Bilirubin, μmol/L	0–17	...	5	...	4	...	34	55	101	108
AF, U/L	40–120	158	158	104	113	...	215	...	...	...
Amylase, U/L	60–220	...	...	...	...	162	...	...	430	65
CRP, mg/L	<5	9	...	81	117	...	...	72	...	...
Ammonia, mmol/L	60–220	...	...	...	...	...	...	...	690	...

**NOTE.** AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; γ-GT, γ-glutamyl transferase; LDH, lactate dehydrogenase; AF, alkaline phosphatase; CRP, C-reactive protein; VCN, voriconazole.

<sup>a</sup> Treatment with VCN therapy was discontinued on day 7.

<sup>b</sup> Treatment with HAART was discontinued on day 12.

<sup>c</sup> The patient died on day 28.

coma. The patient died 28 days after the start of voriconazole therapy. A postmortem investigation was not performed.

**Discussion.** Although fatal adenoviral infections in HIV-infected children have been described [3], a quantitative PCR assay excluded adenovirus dissemination in the patient's blood. In fact, we believe that our patient died from a noninfectious toxic liver failure caused by drug interaction between one or both of the protease inhibitors the patient was receiving and voriconazole. Extensive antiretroviral therapy can induce some hepatotoxicity in children [4] (although this condition occurs more frequently in adults) in the first months after initiation of therapy and in the presence of concomitant chronic viral hepatitis [5]. However, our patient had never been infected with HBV or HCV and had already used the same regimen of HAART for 7 months without any sign of hepatotoxicity until voriconazole therapy was started.

The metabolic impact of the protease inhibitors as a substrate of the cytochrome P450 isoenzymes CYP2C9, CYP3A4, and CYP2C19 has generated concern about hepatotoxicity and the metabolism of other drugs. In vitro studies have shown that voriconazole is a substrate of the aforementioned cytochrome P450 isoenzymes, mostly of CYP2C19 [1]. Protease inhibitors may increase voriconazole plasma concentrations and vice versa. Interactions with reverse transcriptase inhibitors have not been reported [6]. In our patient, the blood levels of the antiretroviral inhibitors were elevated.

In the largest study of voriconazole to date, Walsh et al. [7] concluded that voriconazole was not associated with any increase in the frequency of hepatic abnormalities, compared with liposomal amphotericin B. However, prior use of amphotericin B had not induced any liver dysfunction in our patient. In an efficacy and safety study of voriconazole therapy for invasive

aspergillosis, Denning et al. [8] noted abnormalities in the liver function test results of 10–15% of adult patients receiving voriconazole, starting in the first month—and often in the first 10 days—of therapy. In 6 of 22 patients with plasma concentrations >6000 ng/mL, abnormal liver function or liver failure occurred without reported mortality. These effects on the liver are generally reversible after stopping treatment with the drug [7]. In our patient, voriconazole therapy was stopped after 7 days.

Voriconazole exhibits nonlinear pharmacokinetics [9] and may be influenced by certain polymorphisms in the *CYP2C19* gene. Moreover, the concentrations of voriconazole in children are generally much lower than in healthy adults [10]. Measuring the actual plasma concentrations of voriconazole may therefore be of limited value. Thus, even though the concentration of voriconazole was not measured in our patient, a direct and irreversible interaction with HAART most likely occurred.

Our patient's case warrants caution in combining HAART with medication, such as voriconazole, that is metabolized in a similar way. Monitoring drug levels may seem mandatory for lowering the dosage of or stopping medication under certain conditions, but, irrespective of the actual plasma level, will not always prevent acute liver failure from ensuing after medication is stopped, as is illustrated in our case.

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