Drug-Drug Interaction between Itraconazole and Efavirenz in a Patient with AIDS and Disseminated Histoplasmosis

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Although there is a presumed drug-drug interaction between itraconazole and nonnucleoside reverse-transcriptase inhibitors, the medical literature lacks such documentation. We describe a drug-drug interaction between itraconazole and efavirenz in a patient with disseminated histoplasmosis and acquired immunodeficiency syndrome (AIDS). The drug combination resulted in persistently elevated urinary Histoplasma antigen levels and subtherapeutic plasma itraconazole concentrations. Changing treatment from efavirenz to a protease inhibitor was accompanied by improvements in the desired urinary Histoplasma antigen level and plasma itraconazole concentration.

Case report. A 42-year-old man with a history of AIDS presented to our hospital with respiratory distress and hypotension. The patient had been receiving antiretroviral therapy consisting of efavirenz, lamivudine, and stavudine. Examination of the patient revealed tachycardia, hypotension, 100% oxygen saturation, and absence of fever. Maculopapular lesions were noted on the patient’s forehead. Laboratory investigations revealed pancytopenia (WBC count, 1200 cells/µL; hemoglobin level, 5.6 g/dL; platelet count, 87,000 platelets/µL) and an elevated alkaline phosphatase level and lactate dehydrogenase level, 5.6 g/dL; platelet count, 87,000 platelets/µL) and an elevated alkaline phosphatase level and lactate dehydrogenase level, 5.6 g/dL; platelet count, 87,000 platelets/µL) and an el-

Discussion. Although the incidence of histoplasmosis has decreased in patients with AIDS since the advent of HAART, histoplasmosis still causes significant morbidity and mortality in this patient population. More than 95% of HIV-infected patients who have histoplasmosis will develop the disseminated form of the disease [1].

Itraconazole is an important component of treatment for this opportunistic infection—after induction therapy with amphotericin B and as long-term maintenance therapy for HIV-infected individuals [2]. Although one study demonstrated the safety of discontinuation of maintenance therapy for HIV-infected patients [3], lifelong secondary prophylaxis is still recommended for HIV-infected patients with a history of Histoplasma infection [4]. As a result, it is quite likely that many HIV-infected patients with histoplasmosis will eventually receive both itraconazole and antiretroviral therapy concurrently.
Recent elevation of his urine predominance in this patient, there was concern about the per-eroleoside reverse-transcriptase inhibitor. Despite clinical im-
tuation regarding drug-drug interactions between itraconazole at some point. However, there are very few studies in the lit-
terature describing the interaction between efavirenz and itracona-
ol. This article describes the first known reported case involving
a drug-drug interaction between itraconazole and a nonnu-
cleoside reverse-transcriptase inhibitor. Despite clinical im-
provement in this patient, there was concern about the per-
sistent elevation of his urine Histoplasma antigen level (4.28
U), even after a year of antifungal therapy with itraconazole.
The patient was fortunate, however, that no clinical manifes-
tations of treatment failure or relapse of histoplasmosis were
associated with this elevated Histoplasma antigen level. Some
experts recommend observing the antigen level until it becomes
negative or at least ≤4 U. Close follow-up to monitor for
relapse is advised for patients who have not had a known re-
version to a negative antigen test result [2]. Increases of the
Histoplasma antigen level of ≥2 U have been shown to be a
strong predictor of relapse [5].

In this case, we considered that the lower dose of itraconazole
(200 mg once daily) and use of the capsule formulation may
have resulted in the mildly increased urine Histoplasma antigen
level. Consequently, the patient’s itraconazole dosage was first
increased, with no change in the antigen level, and then changed
to the solution formulation, which also had no effect.

Itraconazole is predominantly metabolized by the cyto-
chrome P450 3A4 (CYP3A4) enzyme to hydroxyitraconazole
and other metabolites [6]. This enzyme pathway also mediates
the metabolism of the nonnucleoside reverse-transcriptase in-
hibitors, including efavirenz and nevirapine [7]. Studies have
shown that, when coadministered, nevirapine induces the me-
tabolism of ketoconazole, leading to reduced ketoconazole bi-
availability [8]. We speculated that efavirenz was causing a
reduced concentration of itraconazole through CYP3A4 en-
zyme induction in a similar fashion. As a result, we changed
the patient’s nonnucleoside reverse-transcriptase inhibitor–
based antiretroviral regimen to a protease inhibitor–based
regimen.

There are a few reports describing the interaction between
protease inhibitors and itraconazole. Commentuy et al. [9]
described how lopinavir-ritonavir increased the concentration
of itraconazole by inhibiting CYP3A4, although no changes in
lopinavir-ritonavir concentrations were seen. We surmised that
the combination of atazanavir and ritonavir would also produce
a similar increase in the itraconazole concentration through
inhibition of this hepatic enzyme pathway. The patient’s lab-
oratory findings were consistent with this drug-drug interac-
tion, with an increase in his plasma itraconazole concentration
from undetectable (<0.05 µg/mL) to 3 µg/mL and a decrease
in his Histoplasma antigen level from 4.28 U to 0.6 U. We
considered this itraconazole concentration to be sufficient, be-
cause Wheat et al. [1] proposed that a therapeutic plasma con-
centration of itraconazole should be at least 2 µg/mL.

As demonstrated by this case report, caution should be taken
when prescribing the combination of efavirenz and itracona-
ol. Careful monitoring of the patient’s clinical status for any
signs of relapse should be performed, because lower bioavail-
ability of itraconazole may be experienced by the patient. Close
follow-up of plasma itraconazole concentrations and Histo-
plasma antigen levels should be considered. If concern about
the efficacy of itraconazole treatment in combination with ef-
virenz arises, a change in antiretroviral therapy to a protease
inhibitor–based regimen is a reasonable option.

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Table 1. Response of the urinary Histoplasma antigen level and plasma itraconazole concentration to changes in treatment in a patient with AIDS and disseminated histoplasmosis.

<table>
<thead>
<tr>
<th>Year, month</th>
<th>CD4 cell count, cells/µL</th>
<th>Viral load, copies/mL</th>
<th>Urinary Histoplasma antigen level, units</th>
<th>Plasma itraconazole concentration, µg/mL</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>50</td>
<td>&lt;400</td>
<td>15</td>
<td>...</td>
<td>EFV, 3TC, d4t; itra capsule (200 mg OD)</td>
</tr>
<tr>
<td>April</td>
<td>60</td>
<td>&lt;400</td>
<td>9.8</td>
<td>...</td>
<td>EFV, 3TC, d4t; itra capsule (200 mg OD)</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>130</td>
<td>&lt;400</td>
<td>4.28</td>
<td>...</td>
<td>EFV, 3TC, d4t; itra capsule (200 mg OD)</td>
</tr>
<tr>
<td>September</td>
<td>140</td>
<td>&lt;400</td>
<td>4.28</td>
<td>...</td>
<td>EFV, 3TC, d4t; itra capsule (200 mg OD)</td>
</tr>
<tr>
<td>October</td>
<td>113</td>
<td>&lt;400</td>
<td>4.28</td>
<td>&lt;0.05</td>
<td>EFV, 3TC, d4t; itra capsule (200 mg BID)</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>106</td>
<td>&lt;400</td>
<td>&lt;0.05</td>
<td>EFV, 3TC, d4t; change to itra solution (200 mg BID)</td>
<td></td>
</tr>
<tr>
<td>April</td>
<td>130</td>
<td>&lt;400</td>
<td>4.28</td>
<td>&lt;0.05</td>
<td>ATZ, rit, emtricitabin, tenofovir; itra solution (200 mg BID)</td>
</tr>
<tr>
<td>June</td>
<td>176</td>
<td>&lt;400</td>
<td>4.28</td>
<td>&lt;0.05</td>
<td>ATZ, rit, emtricitabin, tenofovir; itra solution (200 mg BID)</td>
</tr>
<tr>
<td>July</td>
<td>196</td>
<td>&lt;400</td>
<td>0.6</td>
<td>...</td>
<td>ATZ, rit, emtricitabin, tenofovir; itra solution (200 mg BID)</td>
</tr>
</tbody>
</table>

NOTE. ATZ, atazanavir; BID, twice daily; d4T, stavudine; EFV, efavirenz; itra, itraconazole; OD, once daily; rit, ritonavir; 3TC, lamivudine.

* Changes in treatment were made after the laboratory results were obtained for the corresponding date.
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References