Drug-Drug Interaction between Itraconazole and the Antiretroviral Drug Lopinavir/Ritonavir in an HIV-1–Infected Patient with Disseminated Histoplasmosis

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We describe a drug-drug interaction between coformulated lopinavir/ritonavir and itraconazole in a patient infected with human immunodeficiency virus type 1 who had disseminated histoplasmosis. Coadministration of these agents led to a strong increase in itraconazole concentrations and a decrease in concentrations of its metabolite, hydroxyitraconazole, which is equally active pharmacologically. The dosage of itraconazole was reduced when it was used in combination with lopinavir/ritonavir.

Case report. A 54-year-old man living in the Netherlands underwent surgery for a gastric perforation during a vacation in his native country, Surinam, in South America. The pathology report showed extensive inflammation and ulceration with tissue necrosis, without signs of Helicobacter pylori infection or malignancy. After his return to The Netherlands, the patient was rehospitalized because of persisting abdominal pain, anorexia, weight loss (>25 kg), and fever with night sweats. Serological testing revealed an infection with HIV-1, with a virus load of >1 million RNA copies/mL and a CD4 cell count of 60 cells/μL. Chest radiography showed bilateral interstitial infiltrates. Gastroscopy revealed a gastric ulcer; Histoplasma capsulatum was identified in samples from the ulcer. Moreover, H. capsulatum, as well as Pneumocystis carinii, was isolated from bronchoalveolar lavage fluid. Treatment with cotrimoxazole (2400 mg iv twice daily) and amphotericin B (0.7 mg/kg iv per day) was initiated.

After 7 weeks of treatment, the intravenous amphotericin B therapy was switched to therapy with oral itraconazole solution (200 mg twice daily). Because of the patient’s poor immune status, it was also necessary to initiate antiretroviral treatment quickly. The regimen consisted of the protease inhibitor combination lopinavir/ritonavir (400/100 mg twice daily) and a nucleoside-analogue backbone of lamivudine (150 mg twice daily) and stavudine (30 mg twice daily). However, a drug-drug interaction between the antifungal drug and the protease inhibitor combination was suspected, as a result of the drugs having a similar metabolic route [1]. To study the effects of lopinavir/ritonavir on the plasma concentrations of itraconazole and its equally active metabolite hydroxyitraconazole, our patient underwent extensive pharmacokinetic examination. After 10 days of treatment with itraconazole oral solution, before the start of the antiretroviral therapy, pharmacokinetic profiles of itraconazole and hydroxyitraconazole were composed (figure 1A). Blood samples were drawn during one 12-h dosing interval. The plasma concentrations of itraconazole and its metabolite were determined by high-performance liquid chromatography (HPLC) with fluorescence detection [5]. This procedure was repeated on the second day of antiretroviral treatment (figure 1B) and again 5 weeks after the start of antiretroviral treatment (figure 1C). In addition, the plasma concentrations of lopinavir/ritonavir in these blood samples were measured by liquid chromatography coupled with tandem mass spectrometry [6]. With the initiation of lopinavir/ritonavir treatment, the itraconazole dosage was lowered to 200 mg once daily to avoid potential toxicity resulting from high plasma levels of the antifungal drug.

The measured concentrations of itraconazole and hydroxyitraconazole on the 3 sampling days are shown in figure 1. Before the start of lopinavir/ritonavir therapy, the itraconazole concentrations were lower than the concentrations of the metabolite hydroxyitraconazole (ratio of area under the plasma concentration–time curve values [AUCItr/AUCH-Itr], 0.63; figure 1A). However, after the start of antiretroviral treatment, the parent/metabolite ratio inverted (AUCItr/AUCH-Itr, 1.64; figure 1B). The total exposure to the active antifungal drug on the second sampling day was comparable to the exposure before the start of antiretroviral treatment (AUCItr+H-Itr values, 10,000 and 12,000 ng/h/mL, respectively) although the dose had been...
Figure 1. Plasma concentrations of itraconazole (solid lines) and hydroxyitraconazole (dotted lines) in an HIV-1–infected patient with histoplasmosis. A, Concentrations before the start of antiretroviral therapy, while the patient was receiving itraconazole, 200 mg b.i.d., and no antiretroviral drugs. B, Concentrations on the first day of antiretroviral therapy, while the patient was receiving itraconazole, 200 mg q.d., and lopinavir/ritonavir, 400/100 mg b.i.d. C, Concentrations when antiretroviral therapy was at steady state and the patient was receiving itraconazole, 200 mg q.d., and lopinavir/ritonavir, 400/100 mg b.i.d.

halved. On the third sampling day, after 5 weeks of concomitant administration of lopinavir/ritonavir and itraconazole, the plasma concentrations of lopinavir/ritonavir had reached steady state levels. The delayed metabolic degradation of itraconazole had caused accumulation, leading to itraconazole levels exceeding 2000 ng/mL (figure 1C). The terminal half-life of itraconazole had increased from ~16 h, before initiation of treatment with lopinavir/ritonavir, to >160 h while the patient was receiving maintenance treatment. No signs of itraconazole-related toxicity were observed.

The plasma concentrations of lopinavir and ritonavir at steady state (maximum concentrations were 8.5 and 0.5 mg/L, and concentrations before dosing were 3.4 and 0.1 mg/L, respectively) with concomitant use of itraconazole were not different from concentrations achieved in HIV-infected adults who did not receive concomitant treatment with interacting drugs [2].

The patient in this case was doing well as of December 2003. After 4 months of antiretroviral treatment, the HIV virus load was undetectable (<50 RNA copies/mL) and CD4 cell count had increased from 60 to 310 cells/μL. There were no signs of reactivation of the infection with H. capsulatum.

Discussion. The optimal treatment of disseminated histoplasmosis today consists of an induction phase with intravenous amphotericin B (0.7–1 mg/kg daily) followed by therapy with oral itraconazole (200 mg twice daily) [7]. For patients with AIDS, long-term maintenance therapy with itraconazole is required after a severe manifestation of the infection to prevent relapses [7].

In this case, the treatment with itraconazole in combination with antiretroviral drugs was monitored with drug concentration measurements to prevent toxicity or subtherapeutic concentrations. Lopinavir and ritonavir are metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme [2]. This enzyme also catalyzes the conversion of itraconazole to its metabolite hydroxyitraconazole, which has antifungal activity comparable to the parent compound in vitro [3]. Ritonavir and itraconazole are both inhibitors of CYP3A4, but ritonavir is also able to induce the enzyme. Therefore, coadministration of lopinavir/ritonavir and itraconazole may alter the plasma concentrations of lopinavir/ritonavir as well as the ratio of itraconazole to hydroxyitraconazole. The effect of lopinavir/ritonavir on the pharmacokinetics of itraconazole and vice versa, however, has not been described in detail in the available literature. MacKenzie-Wood et al. [1] briefly mentioned the potential interaction between itraconazole and HIV protease inhibitors. An interaction study in healthy volunteers has been performed with the itraconazole analogue ketoconazole and reported in abstract form [4]. Ketoconazole is a very potent inhibitor of CYP3A4, similar to itraconazole, but had no significant effect on the pharmacokinetics of lopinavir. The concentration of ketoconazole was increased 3-fold when lopinavir/ritonavir was coadministered.

In our patient, hydroxyitraconazole levels exceeded itraconazole levels before the start of lopinavir/ritonavir therapy, at day 11 of itraconazole treatment (figure 1A), as described elsewhere [3, 8, 9]. However, the concentrations of the parent compound, as well as the metabolite, were lower than reported in prior studies [8], suggesting that steady state concentrations might not have been achieved. Immediately after the start of lopinavir/ritonavir therapy, the concentrations of itraconazole
remained at the same level, despite the dose reduction, whereas hydroxyitraconazole concentrations were significantly decreased (figure 1B). This was probably caused by inhibition of CYP3A4 by lopinavir/ritonavir, which swiftly decreased the formation of hydroxyitraconazole from itraconazole. Since lopinavir and ritonavir were coadministered, it cannot be concluded from these data whether the enzyme inhibition was caused by ritonavir or lopinavir, or by both. After 5 weeks of concomitant treatment, accumulation had resulted in itraconazole concentrations exceeding 2000 ng/mL (figure 1C). Ritonavir may have inhibited the gastric motility, inducing a prolonged irregular absorption phase, which was especially pronounced on this occasion. The concentrations of lopinavir/ritonavir were not altered by concomitant administration of itraconazole, indicating that lopinavir/ritonavir may be a stronger inhibitor of CYP3A in vivo than itraconazole. The achieved antifungal drug concentrations were probably sufficiently high for optimal treatment. Hecht et al. [10] and Wheat et al. [11] have proposed a therapeutic concentration of itraconazole in the treatment of disseminated histoplasmosis of 2000 ng/mL. This target was, however, based on concentrations measured with a bioassay, and thus represents the combined levels of itraconazole and hydroxyitraconazole. Applying this target to concentrations measured by HPLC with fluorescence may not be justified. No target concentrations measured with HPLC with fluorescence were described for patients with histoplasmosis. However, considering the available data, the concentrations antifungal drugs achieved in the patient we describe appear to be adequate to prevent a relapse of the infection. Therefore, it seems valid to use itraconazole oral solution at a dosage of 200 mg once daily in combination with lopinavir/ritonavir at a dosage of 400/100 mg twice daily for maintenance treatment of disseminated histoplasmosis. However, since long-term maintenance treatment with itraconazole is necessary, it is important to continue the close monitoring of the treatment and the plasma concentrations, especially when dosages or concomitantly administered drugs are altered.

References