Nelfinavir, a Protease Inhibitor, Increases Sirolimus Levels in a Liver Transplantation Patient: A Case Report

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With the increasing success of liver transplantation and the proven effectiveness of highly active retroviral therapy in HIV-positive patients, liver transplantation has been performed successfully in selected HIV-positive recipients with CD4 and an HIV viral load response to highly active antiretroviral therapy. In these patients, an interaction between a protease inhibitor (nelfinavir) and tacrolimus has been shown. The effect of nelfinavir on the pharmacokinetics of sirolimus, a newer immunosuppressive drug, is currently not known. The goal of the present case report is to document the interaction between sirolimus and nelfinavir in a liver transplantation patient. A 40-year-old woman who was HIV positive underwent a cadaveric liver transplantation for acute fulminant liver failure secondary to nevirapine (a nonnucleoside reverse transcriptase inhibitor). Postoperatively, she was treated with tacrolimus and steroids. She experienced steroid-resistant rejection and was started on sirolimus on the 17th postoperative day. Kinetic parameters were determined after a 2-mg oral dose of sirolimus and 250 mg of nelfinavir by collecting multiple peripheral venous blood samples before and after sirolimus administration. The kinetic parameters were compared with parameters from three liver transplantation patients on sirolimus who were not on nelfinavir. After normalizing the kinetic parameters to sirolimus dose of 1 mg/d, 0-hour and 24-hour trough sirolimus concentrations were nine-fold and five-fold higher for the patient who was on nelfinavir, compared with those who were not on nelfinavir. The maximum concentration was 3.2 times higher, the area under the concentration curve was 1.6 times higher, and the terminal disposition half-life was prolonged by 60%. The time to reach the peak concentration was 1 hour in all patients. Increase in trough concentration, peak concentration area under the curve concentration, and prolongation of half-life of sirolimus has been shown in a patient who was on a low dose (one fifth the recommended dose) of nelfinavir. (*Liver Transpl 2002;8:838-840.*)

Successful liver transplantation has been performed in HIV-positive patients.[1,2] However, these patients must continue highly active antiretroviral therapy after transplantation to manage their HIV infections. Because the use of antiretroviral drugs has been associated with significant drug interactions,[3] caution is required in the management of the immunosuppressive drug therapy in these patients. The protease inhibitor nelfinavir has recently been documented to drastically decrease the dose of tacrolimus required to maintain adequate trough blood concentrations in a liver transplantation patient.[4] Sirolimus is a newer immunosuppressive drug that seems to be beneficial in liver transplantation patients.[5,6] The potential effect of nelfinavir on the blood concentrations of the sirolimus is not known. In the present case report, we document an interaction between nelfinavir and sirolimus in a liver transplantation patient.

Case Report

A 40-year-old woman who was diagnosed with HIV on routine testing had a CD4 count of 68 and a low viral load. She received azidothymidine, lamivudine, and nevirapine. She responded well initially, with a CD4 count of 103. However, 4 weeks later she presented with acute fulminant liver failure. A liver biopsy showed massive hepatic necrosis. She underwent successful orthotopic liver transplantation on May 2000. Her antiretroviral therapy was withheld perioperatively. Her initial immunosuppressive therapy consisted of one gram intravenous methylprednisolone on reperfusion of the liver followed by a 6-day steroid taper from 200 to 20 mg/d. She also received tacrolimus (0.3 mg/kg/d) intravenously for a few days, and then was switched to oral tacrolimus 0.15 mg/kg/d. On the 17th postoperative day, she experienced mild-to-moderate acute cellular rejection, which was treated with steroids,

and she was started on sirolimus (5 mg/d). Her antiretroviral therapy was also reinitiated with lamivudine, zidovudine, and nelfinavir. Nelfinavir was started at a dose of 250 mg twice per day (one fifth of the regular dose), which was increased to 750 mg three times per day by 3 months, and currently she is on 1250 mg twice per day. Three weeks after the initial low dose of nelfinavir, her platelet count decreased from 321×106 L to 144×106 L; the white cell count decreased from 12.4×106 L to 2.9×106 L; and the hematocrit decreased from 34.9% to 29.1%. At this time, the 24-hour trough blood concentration of sirolimus was 24.7 ng/mL. The dose of sirolimus was decreased to 3 mg/d and then to 2 mg/d. The pharmacokinetics of sirolimus were evaluated 5 days later by collecting 3 mL of blood at 0 (before the dose of sirolimus), 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the 2-mg oral dose of sirolimus. A similar pharmacokinetics evaluation of sirolimus was performed in three other liver transplantation patients who were on a stable dose of 5 to 7 mg/d sirolimus who were not receiving nelfinavir. Sirolimus levels were measured by the high-pressure liquid chromatography–mass spectrometry/massspectrometry method.[7] Sirolimus pharmacokinetics parameters including trough concentrations (0-hour and 24-hour), maximum blood concentrations, time to reach maximum concentration, the terminal disposition half-life, and the area under the concentration curve from 0-24 hours were compared between the patient on nelfinavir therapy and those not on nelfinavir.

Results

The liver and renal function were normal in the patient who received nelfinavir on the day of the pharmacokinetic evaluation (total bilirubin, 0.6 mg/dL; alanine aminotransferase, 30 μ/L; alkaline phosphatase, 18 μ/L; alkaline phosphatase, 70 μ/L; γ-glutamyltransferase, 69 μ/L; blood urea nitrogen, 15 mg/dL; creatinine, 0.9 mg/dL). The three other patients not receiving nelfinavir had bilirubin levels of 1.4, 1.7, and 2.1 mg/dL. The whole blood concentration versus time profile for sirolimus in the patient on nelfinavir is shown in Figure 1 along with the median blood concentration versus time profile in the three patients not receiving nelfinavir therapy, after normalizing the values to a 1-mg dose of sirolimus. The 0-hour and 24-hour trough blood concentrations were 5.3 ng/mL and 4.6 ng/mL for the study patient versus the mean concentration of 0.58 ± 0.4 (median, 0.57) and 0.94 ± 0.8 ng/mL (median, 0.94) for the control group (ninefold and five-fold higher, respectively). The time to
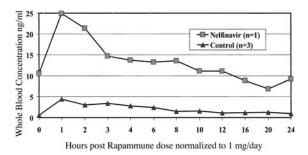

Figure 1. Whole blood concentration of sirolimus versus time in a patient who was on nelfinavir versus the median blood concentrations of sirolimus in patients (n = 3) who were not on nelfinavir. The concentrations represented are normalized to a 1-mg dose of sirolimus.

reach maximum concentration (1-hour) was not different in the study patient and the control group. The maximum concentration was 12.5 ng/mL in the study patient compared with 3.87 ± 1.97 ng/mL in the control group (3.2-fold higher). The terminal disposition half-life in the patient was 22 hours, and that for control group was 12.4 hours (median half-life) or 15.6 hours (mean half-life). The area under the concentration curve 0 to 24 hours was 49 ng/mL/h/mg in the study patients versus 30.5 ± 11.6 ng/mL/h/mg (60% higher for study patient) in the control group.

Discussion

Multiple drug interactions have been reported with the use of antiretroviral drugs.[3,8-11] Nelfinavir is a substrate for the P4503A4/5 system and is known to inhibit the metabolism of several other drugs.[8-11] Nelfinavir is a substrate and inhibitor of p-glycoprotein efflux pump.[12,13] In clinical use, increased concentrations of coadministered drugs are often observed in patients on nelfinavir because of inhibition of CYP3A4/5 enzyme and/or p-glycoprotein efflux pump.

Tacrolimus is metabolized by the cytochrome P4503A4/5 system and is a substrate for p-glycoprotein.[14-16] Nelfinavir has been observed to inhibit the metabolism of tacrolimus and substantially decrease the dose of tacrolimus required in a liver transplantation patient.[4] Sirolimus is a substrate for CYP3A4/5 and p-glycoprotein.[15,17] Therefore, we also anticipated a nelfinavir-mediated increase in sirolimus levels in our patient. In the present report, even with one fifth of the recommended dose of nelfinavir, there was a significant increase in the blood concentrations of sirolimus in our patient compared with three other patients who were not on nelfinavir. The present case report provides a

basis for further kinetic studies to evaluate the interaction between nelfinavir and sirolimus and to establish an appropriate dosing regimen of sirolimus in patients on drugs such as nelfinavir. In the meantime, frequent monitoring of the trough concentrations of sirolimus is recommended to avoid sirolimus-mediated toxicity in patients who simultaneously receive nelfinavir.

Conclusion

Even with one fifth of the recommended dose of nelfinavir, a nine-fold increase in sirolimus trough concentration, three-fold increase in peak concentration, and 60% increase in area under the concentration curve 0 to 24 hours has been observed in a liver transplantation patient, compared with patients who were not on nelfinavir. Caution is suggested when these drugs are used together until additional kinetic studies are performed and a better understanding of the interaction between the agents emerges.

Acknowledgment

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