

Case Report

Phenytoin Decreases the Blood Concentrations of Sirolimus in a Liver Transplant Recipient: A Case Report

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Summary: This report documents that coadministration of phenytoin leads to decreased blood concentrations and area under the blood concentration–time curve of sirolimus in a liver transplant patient. It is essential to monitor the blood concentrations of sirolimus and adjust the sirolimus dosage when phenytoin administration begins or ends. **Key Words:** Phenytoin—Sirolimus—Liver transplantation.

Sirolimus is a novel immunosuppressive drug that appears to be beneficial in preventing rejection and minimizing nephrotoxicity in liver transplant patients (1,2). Sirolimus is metabolized by cytochrome P450 3A4/5 enzyme system (3). Certain drugs, such as phenytoin and rifampin, increase the activity of CYP3A4/5 enzyme. Higher doses of immunosuppressive agents, such as cyclosporin and tacrolimus, which are metabolized by the cytochrome P450 system, are required to maintain therapeutic drug concentrations in patients who concurrently receive phenytoin, a CYP3A4/5 inducer (4–7). Recently, the need to use a large dose of sirolimus in a pediatric kidney transplant patient who received phenytoin was reported (8). The aim of this report is to examine the interaction between phenytoin and sirolimus by measuring sequential trough blood concentrations of sirolimus and the pharmacokinetic changes following introduction and subsequent discontinuation of phenytoin in a liver transplant patient on sirolimus therapy.

CASE REPORT

A 62-year-old diabetic woman who originally presented with a combination of autoimmune hepatitis and primary biliary cirrhosis underwent orthotopic liver transplantation on December 21, 2001. The recipient's early postoperative course was initially uncomplicated. Approximately 1 week posttransplantation the patient developed a seizure disorder with an altered mental status and a decreased level of consciousness. Magnetic resonance imaging (MRI) revealed diminished subcortical white matter with increased T2 signal in the remainder of the subcortical white matter, which had increased in number and size compared with a prior study. Electroencephalogram was markedly abnormal with disorganization of background activity and superimposed intermittent periodic discharges, which were maximal in the left hemispheric region but frequently generalized.

The patient was treated postoperatively with tacrolimus-based immunosuppression. At the time of neurologic deterioration, she was placed on intravenous phenytoin, and tacrolimus was replaced with cyclosporin (200 mg/d). Cyclosporin was subsequently discontinued due to persistence of her neurologic state, and she was started on sirolimus therapy (5 mg/d). Sirolimus levels

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TABLE 1. Laboratory values on day 21 (while on phenytoin) and on day 41 (10 days following discontinuation of phenytoin)

	Day 29	Day 41
T. bilirubin (mg/dL)	0.20	0.20
Aspartate aminotransferase (IU/L)	42	34
Alanine aminotransferase (IU/L)	33	13
Urea (mg/dL)	60	54
Creatinine (mg/dL)	0.80	0.90
FK (ng/mL)	4.0	3.8
Hemoglobin (g/dL)	8.3	11.4
Hematocrit (%)	24.7	33.1
White blood cells ($\times 10^9/L$)	15.6	5.6
Platelets ($\times 10^9/L$)	353	296

were subtherapeutic, requiring escalation of the dosage to 15 mg/d.

Sirolimus pharmacokinetic analysis was evaluated during (day 29 posttransplant) and 10 days after discontinuation (day 41 posttransplantation) of phenytoin therapy. Three-milliliter samples of blood were drawn in purple-top vacutainers at times 0 (24-hour trough level, prior to sirolimus dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours following oral sirolimus dose. The samples were analyzed by high-performance liquid chromatography–mass spectrometric assay (HPLC-MS) (9), and various pharmacokinetic parameters were calculated as per standard methods.

RESULTS

The laboratory values at the two time points were similar and are summarized in Table 1. The patient received phenytoin dose of 100 mg twice daily with a trough plasma level of 5.5 $\mu\text{g/mL}$. The 24-hour trough

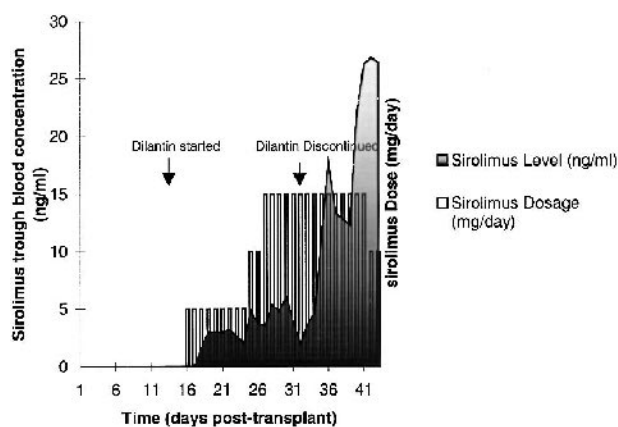


FIG. 1. Sirolimus concentrations (ng/mL) and daily dosages (mg/d) throughout the study period. Arrows indicate initiation and subsequent discontinuation of intravenous phenytoin therapy (100 mg twice daily).

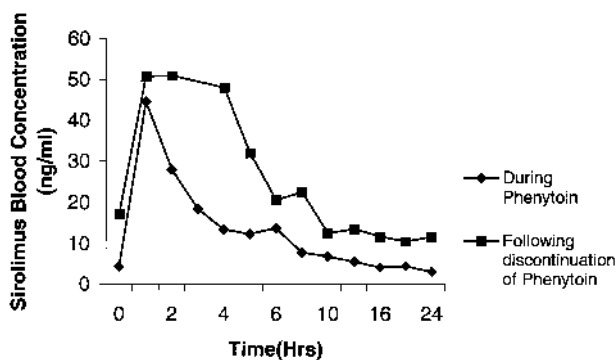


FIG. 2. Sirolimus blood concentration versus time data over one dosing interval during and after discontinuation of phenytoin therapy.

concentrations of sirolimus increased from <5 ng/mL to 15 to 20 ng/mL following discontinuation of phenytoin (Fig. 1). The sirolimus C_0 , C_{\max} , and C_{24} concentrations increased from 4.4 ng/mL, 44.6 ng/mL, and 3.1 ng/mL to 17.2 ng/mL, 51 ng/mL, and 11.7 ng/mL, respectively, after discontinuation of phenytoin. The time to reach peak blood concentration (T_{\max}) was essentially the same. The apparent disposition half-life measured during a dosing interval increased from 10.2 to 22.4 hours after discontinuation of phenytoin. The area under the blood concentration–time curve ($AUC_{0-\infty}$) for that given dose as calculated using reverse superposition principle increased from 207 to 341 ng/mL/h after discontinuation of phenytoin (Fig. 2).

DISCUSSION

Our observations clearly suggest that phenytoin, a potent inducer of the CYP3A4/5, increased the metabolism of sirolimus and decreased sirolimus exposure in this patient. As sirolimus is metabolized in the liver and in the intestine, phenytoin could have increased the metabolism of sirolimus at both sites. Our observations are similar to that observed with cyclosporin and phenytoin. The increase in trough blood concentrations and AUC after discontinuation of phenytoin may partially be related to the increase in hematocrit, as sirolimus is known to be bound to red blood cells. In any event, it is extremely important to monitor the blood concentrations of sirolimus and adjust the dosage when phenytoin is given to patients on sirolimus therapy. It is particularly important to do so when sirolimus is used as a primary immunosuppressive agent without calcineurin inhibitors in the early course of clinical transplantation when the incidence of rejection is higher.

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