A Potentially Significant Interaction between Efavirenz and Phenytoin: A Case Report and Review of the Literature

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Although it has not been demonstrated yet, phenytoin is expected to reduce efavirenz exposure through coinduction of cytochrome P450 (CYP) 3A4 and CYP2B6. Conversely, efavirenz has been shown in vitro to inhibit the enzymes responsible for phenytoin metabolism, CYP2C9 and CYP2C19. We report a case in which a potential bidirectional drug interaction between phenytoin and efavirenz resulted in lower-than-expected efavirenz concentrations and elevated phenytoin levels. Therapeutic drug monitoring was used in this case to ensure adequate efavirenz exposure.

Antiretrovirals are widely known for their pharmacokinetic drug interactions. Most of the attention has been focused on the role of cytochrome P450 (CYP) isoenzyme modulation in interactions involving protease inhibitors and nonnucleoside reverse-transcriptase inhibitors (NNRTIs). Like protease inhibitors, NNRTIs are metabolized by CYP3A4. However, their effects on the isoenzyme differ—delavirdine is a potent inhibitor, nevirapine is a potent inducer, and efavirenz (EFV) is a mixed inhibitor and inducer of CYP3A4. As a mixed inducer and inhibitor, the effect of EFV on coadministered CYP3A4 substrates is unpredictable. In addition to its modulation of CYP3A4, EFV has been shown to inhibit CYP2C9 and CYP2C19 in vitro [1, 2]. EFV is metabolized principally by CYP2B6 and, to a lesser degree, by CYP3A4 [1, 3]. Concurrent use of medications that alter these metabolic pathways may affect EFV exposure.

As an inducer of CYP3A4, phenytoin may cause significant reductions in protease inhibitor and NNRTI concentrations during coadministration. Results from a pharmacokinetic study conducted in healthy volunteers who received lopinavir in combination with ritonavir revealed a 2-way interaction in which the area under the concentration-time curves (AUCs) for both phenytoin and lopinavir were decreased by ~30% [4]. Although it has not been demonstrated yet, phenytoin is expected to reduce EFV concentrations as well.

We report a case in which a potential drug interaction resulted in lower-than-expected EFV concentrations after initiation of an antiretroviral treatment regimen in a patient who was receiving phenytoin. Therapeutic drug monitoring was used in this case to ensure adequate EFV exposure.

CASE REPORT

In July 2004, a 39-year-old Ethiopian man was admitted to a hospital (not ours) with new-onset seizures. The medical evaluation included MRI, the findings of which showed multiple contrast-enhancing lesions in the cerebrum and cerebellum. The patient was also found to have serum anti-toxoplasma IgG antibodies and a CD4 cell count of 49 cells/mm3 (CD4 cell percentage, 5.5%). A presumed diagnosis of toxoplastic encephalitis was made, and therapy with pyrimethamine and sulfadiazine was started. Prophylaxis with trimethoprim-sulfamethoxazole and azithromycin was initiated presumptively for prevention of Pneumocystis jiroveci pneumonia and

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EFV concentration of 0.34 μg/mL after dosing, and the test result, returned 10 days later, was an unexpected lower-than-expected concentration (12-h plasma concentrations range from 0.13 to 15.2 μg/mL). Despite an early virologic response (the HIV RNA load decreased to 30,863 copies/mL after 13 days of antiretroviral therapy), it was thought that persistent inadequate EFV exposure might put the patient at risk for treatment failure. After consultation with the neurology service, the decision was made to rapidly taper the phenytoin dosage and to commence therapy with levetiracetam—an anticonvulsant without CYP modulation potential. The EFV dosage was increased to 800 mg/day under the assumption that CYP induction would continue for 7–14 days after discontinuation of phenytoin therapy.

Prior to implementation of the EFV dosage increase on 12 October, an additional sample was obtained 12-h after dosing, and the test result was an EFV concentration of 0.58 μg/mL. The patient received his last dose of phenytoin on 22 October, after a rapid titration of levetiracetam to 1000 mg twice daily. Obtaining of a sample for a third measurement of EFV level was planned for 9 November, after what was predicted to be sufficient time for reversal of phenytoin’s enzyme induction. The result for the 9 November sample returned 2 weeks later and was an EFV concentration of 2.5 μg/mL. At that time, it was decided that the EFV dosage could be safely reduced to 600 mg/day. On 16 November, the patient had an HIV RNA level of 189 copies/mL and a CD4 cell count of 100 cells/mm³ (CD4 cell percentage, 12%), which indicated continued virologic response to antiretroviral therapy. The patient’s latest measured EFV level, after 3 weeks at a dosage of 600 mg/day, was 1.96 μg/mL.

Phenytoin levels measured after EFV therapy initiation showed a gradual increase, despite a stable phenytoin dosage and no additional changes in medications. After a steady state was achieved, phenytoin plasma concentrations continued to increase after 24 September, gradually increasing to 17 mg/L (on 28 September), 16.7 mg/L (on 29 September), and 23.5 mg/L (on 12 October) (table 1).

DISCUSSION

EFV exhibits linear pharmacokinetics, with concentrations increasing in proportion to increases in dose [1]. It has a long plasma half-life that ranges from 40 to 55 h at steady state [1]. Since EFV is typically taken at bedtime, blood sampling is usually performed 10–16 h after dosing. Because of its long elimination half-life, EFV levels measured around the mid-interval are minimally influenced by sampling time, which contributes only 3% to total concentration variance [5]. Variability in EFV concentrations is largely due to its high interpatient variability (coefficient of variation [CV], 118%) [5]. In contrast, its intrapatient variability is significantly lower (CV, 30%) [5]. EFV 14-h plasma concentrations range from 0.13 to 15.2 μg/mL (median, 2.19 μg/mL) [5].

Data have demonstrated a potential relationship between EFV exposure and virologic response, although there is disagreement in the literature regarding the relationship between EFV concentrations and CNS toxicity [5–9]. Results from a study of the association between 14-h EFV levels with viral suppression and CNS toxicity suggest a potential target concentration range of 1–4 μg/mL [5]. Similarly, results from a retrospective analysis indicate a significant relationship between treatment failure and minimum plasma concentrations of <1.1 μg/mL [6]. Another group of investigators has proposed a higher target concentration of 2.2 μg/mL on the basis of their
Efavirenz and Phenytoin Drug Interaction

Table 1. Results of drug monitoring for a patient who received efavirenz and phenytoin.

<table>
<thead>
<tr>
<th>Date in 2004</th>
<th>Efavirenz dosage a</th>
<th>Efavirenz level, μg/mL</th>
<th>Phenytoin dosage b</th>
<th>Phenytoin level, mg/L</th>
<th>Albumin level, g/dL c</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 Sep</td>
<td>...</td>
<td>...</td>
<td>300 mg q.d.</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>17 Sep</td>
<td>...</td>
<td>...</td>
<td>300 mg po q.d. a</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>19 Sep</td>
<td>...</td>
<td>...</td>
<td>↑ 300 mg b.i.d.</td>
<td>11</td>
<td>...</td>
</tr>
<tr>
<td>22 Sep</td>
<td>600 mg q.d.</td>
<td>...</td>
<td>300 mg b.i.d.</td>
<td>11.5</td>
<td>3.6</td>
</tr>
<tr>
<td>23 Sep</td>
<td>600 mg q.d.</td>
<td>...</td>
<td>300 mg b.i.d.</td>
<td>13.7</td>
<td>3.5</td>
</tr>
<tr>
<td>24 Sep</td>
<td>600 mg q.d.</td>
<td>...</td>
<td>300 mg b.i.d.</td>
<td>14.2</td>
<td>3.6</td>
</tr>
<tr>
<td>28 Sep</td>
<td>600 mg q.d.</td>
<td>...</td>
<td>300 mg b.i.d.</td>
<td>17</td>
<td>3.6</td>
</tr>
<tr>
<td>29 Sep</td>
<td>600 mg q.d.</td>
<td>...</td>
<td>300 mg b.i.d.</td>
<td>16.7</td>
<td>...</td>
</tr>
<tr>
<td>30 Sep</td>
<td>600 mg q.d.</td>
<td>0.34</td>
<td>300 mg b.i.d.</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>12 Oct</td>
<td>↑ 800 mg q.d.</td>
<td>0.58</td>
<td>300 mg b.i.d.</td>
<td>23.5</td>
<td>...</td>
</tr>
<tr>
<td>22 Oct</td>
<td>800 mg q.d.</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>9 Nov</td>
<td>800 mg q.d.</td>
<td>2.5</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>23 Nov</td>
<td>↓ 600 mg q.d.</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>14 Dec</td>
<td>600 mg q.d.</td>
<td>1.96</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

a The up arrows indicate increases in dosages; the down arrow indicates a decrease in dosage.
b Therapeutic range for phenytoin level, 10–20 mg/L.
c Normal range for albumin level, 3.7–4.7 g/dL.
d Plus fosphenytoin iv.
e Therapy discontinued.

finding that patients with 10- to 24-h postdose EFV levels above this limit had at least an 80% response rate [9].

As mentioned above, EFV is extensively metabolized by CYP2B6 and CYP3A4. Drugs that significantly inhibit or induce either of these enzymes are expected to alter EFV concentrations. Voriconazole, for instance, has been shown to increase EFV levels by 44% as a result of CYP3A4 inhibition [1]. Conversely, concurrent administration of rifampin, a potent inducer of CYP3A4 and CYP2B6 was found to reduce the AUC of EFV by 26% [1].

Induction of CYP3A4 by phenytoin is not as strong as induction by rifampin, as demonstrated in vitro. Recent evidence, however, suggests that CYP2B6 induction may play a contributory role in phenytoin interactions [10]. Several studies have found a large degree of cross-regulation between CYP2B6 and CYP3A4 expression, and increases in CYP2B6 activity have been demonstrated with the use of several drugs that are known inducers of CYP3A4 [11–13]. A recent investigation using human hepatocyte cultures characterized phenytoin as a strong inducer of CYP2B6 expression, along with rifampin, clotrimazole, and phenobarbital [13]. Although it has not been reported yet in vivo, coinduction of CYP2B6 and CYP3A4 is expected to result in a reduction in EFV exposure during concurrent use of phenytoin.

Evaluation of drug interactions and studies of individual cases must be done with an awareness of the potential contribution of pharmacogenetics. Patients homozygous for the CYP2B6 T/T genotype at position 516 have greater EFV exposure and an increased incidence of CNS symptoms during their first week of therapy, compared with those of individuals with the G/G or G/T genotype [14, 15]. Likewise, the allelic variants CYP2C9*2 and CYP2C9*3 are associated with phenytoin toxicity and lower dosage requirements [16]. The CYP2B6 T/T genotype is more common among African Americans (prevalence, 20%) than among whites (prevalence, 3%) [14]. In contrast, the CYP2C9*2 and CYP2C9*3 variants are more common among white populations (prevalence, 8%–19% and 3.3%–16%, respectively) than among African American or Ethiopian populations (prevalence, 3.2% and 1.3%, respectively) [17]. At this time, it is not entirely clear the extent to which pharmacogenetics contribute to cases of significant drug interactions. In this case, however, it is likely that the patient had neither CYP2B6 nor CYP2C9 polymorphisms, as evidenced by his dosages and plasma concentrations of phenytoin and EFV.

The increase in phenytoin plasma concentrations in this case was possibly the result of inhibition of CYP2C9 and CYP2C19 by EFV. With a half-life of ~22 h, phenytoin levels measured after 24 September likely reflect steady-state conditions (≥5 days after the bolus and dose increase) [18]. As discussed previously, in vitro studies have shown that EFV inhibits CYP2C9 and CYP2C19 isoenzymes, with K\textsubscript{i} values in the range of observed EFV plasma concentrations (2.7–5.4 μg/mL) [1]. Interpretation of this interaction may be complicated by the concurrent use of sulfadiazine, which has been shown elsewhere to decrease phenytoin clearance by 45%, prolonging its half-life by 80% [19]. However, because sulfadiazine therapy was initiated on 16 September and remained unaltered throughout the duration of events, it is unlikely that it was responsible for...
the increase in phenytoin levels that occurred after 24 September.

Further data on potential EFV target concentrations are needed before therapeutic drug monitoring of EFV becomes standard practice. Nevertheless, EFV concentration monitoring may be helpful in situations in which potential drug interactions, drug toxicity, or the patient’s clinical condition warrants its use. Although a full pharmacokinetic study is needed to confirm or disprove the hypothesis generated by this case report, the events outlined above suggest the potential for a clinically significant 2-way interaction between EFV and phenytoin. Until more data become available, both phenytoin and EFV levels should be monitored closely when the drugs are given concurrently, to avoid potential toxicity or treatment failure.

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References