Status Epilepticus Resulting From Severe Efavirenz Toxicity in an HIV-Infected Patient

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By AIDS Reader

We present the case of an HIV-infected patient with cirrhosis in whom severe neuropsychiatric signs and symptoms developed in the setting of a significantly elevated plasma efavirenz level.

Efavirenz is an NNRTI that is a preferred component of initial therapy for persons infected with HIV-1. It is a potent medication with a long half-life, which allows for once-daily dosing. However, the pharmacokinetics of efavirenz demonstrate high rates of interindividual variability, which may result in variable plasma drug levels.

In addition, high plasma drug levels in patients who are slow metabolizers of efavirenz correlate with drug toxicity and may contribute to early discontinuation of efavirenz-containing regimens. In these patients, plasma efavirenz levels decline significantly more slowly than levels of the companion antiretrovirals, and patients are exposed to a period of effective monotherapy, which increases the risk of selecting for efavirenz resistance.

CASE REPORT
The patient is a 45-year-old woman with a long-standing history of HIV infection and hepatitis C. She first received a diagnosis of HIV/AIDS in 1994 when she presented to an outside hospital with shortness of breath and left-sided weakness. Her initial CD4+ cell count was 70/µL; her HIV RNA level is not known.
Pneumocystis jiroveci (carinii) pneumonia was diagnosed, and she responded well to treatment.

MRI of the brain revealed white matter changes characteristic of progressive multifocal leukoencephalopathy (PML); stereotactic brain biopsy showed gliosis. During the initial hospitalization, her left-sided weakness progressed to a severe spastic hemiparesis. In subsequent months, she had episodes of repetitive left-sided muscle contractions, without alteration of consciousness, which were felt to be partial simple seizures. An electroencephalogram revealed right-sided focal sharp activity. The episodes were controlled with carbamazepine and clonazepam initially and subsequently (1995 onward) with clonazepam alone.

Of note, hepatitis C also was diagnosed in 1994. The patient was treated with interferon alfa and ribavirin in 2000 and with peginterferon alfa and ribavirin in 2003, but her hepatitis C persisted and progressed to cirrhosis.

After her HIV diagnosis in 1994, the patient was treated with zidovudine, with the subsequent addition of didanosine and lamivudine. Over the next several years, with the introduction of protease inhibitors (PIs) and NNRTIs, she was treated with a variety of regimens, although several of these had to be stopped or changed because of adverse effects. In particular, in 1999, nevirapine was stopped because of the development of a rash, and efavirenz was discontinued because of increased muscle spasms and worsening depression.

She was subsequently treated with a stable, but nonsuppressive, regimen of zidovudine, lamivudine, nelfinavir, and saquinavir. She had a declining CD4+ cell count (nadir, 18/µL in 2005) and increasing HIV RNA level (272,000 copies/mL). A genotype and phenotype indicated extensive resistance to NRTIs as well as PIs, but no resistance to NNRTIs. Her regimen was changed to tenofovir, emtricitabine, efavirenz, ritonavir-boosted tipranavir, and enfuvirtide. Within 4 months, the patient’s CD4+ cell count had increased to 159/µL and her HIV RNA level was undetectable (less than 50 copies/mL).

Although the patient had clear immunological and virological improvement, she began to have new untoward symptoms over this period. She reported a progressive increase in anxiety, muscle spasms, and confusion—worse in the mornings—as well as weight loss. In 2006, 4 months after starting her new regimen, she was admitted to the hospital for generalized weakness, confusion, and suspected seizures with bilateral involuntary contractions.

While hospitalized, she had multiple witnessed generalized tonic-clonic seizures and was evaluated by the neurology service. Her seizures were initially very difficult to control; status epilepticus
developed, and she was treated with both valproic acid and levetiracetam. She also had dysphagia, dysarthria, insomnia, hallucinations, and paranoia. Laboratory workup at that time revealed normal blood results, pancytopenia (present since 2003 and thought to be related to her liver disease), and stable liver function test results (2 to 3 times upper limit of normal). MRI of the brain revealed the following: “The brain parenchyma demonstrates T2 hyperintensity and encephalomalacia in the periventricular and subcortical white matter of the bilateral parietal, occipital, and frontal lobes, greater on the right. These findings are stable when compared with the prior examination and are consistent with the given history of PML.” A lumbar puncture revealed normal protein and glucose levels, with no red blood cells or white blood cells. Results were also negative for the following tests on the cerebrospinal fluid (CSF): Cryptococcus antigen; VDRL; and polymerase chain reaction assay for cytomegalovirus, JC virus, varicella-zoster virus, herpes simplex virus, and human herpesvirus 6.

A plasma efavirenz level, obtained approximately 12 hours postdose, was 29,440 μg/L by mass spectrometry (the stated reference range is 1200 to 7000 μg/L). Dysphagia necessitated the discontinuation of antiretrovirals, including efavirenz, and the patient’s mental status improved. A percutaneous gastrostomy feeding tube was placed, and her HIV treatment regimen was restarted, although the efavirenz dosage was lowered to 200 mg daily. Hallucinations and insomnia recurred within several days of restarting this medication, and efavirenz was again stopped. The patient’s dysphagia, dysarthria, confusion, seizures, and hallucinations resolved completely over the ensuing weeks. Her gastrostomy tube was removed 7 weeks after it was placed. She continued her regimen of tenofovir, emtricitabine, tipranavir, ritonavir, and enfuvirtide and has maintained an undetectable HIV RNA level and stable CD4 count.

**DISCUSSION**

**What Are the Neuropsychiatric Adverse Effects of Efavirenz, and Was This Patient’s Presentation Consistent With Efavirenz Toxicity?**

Adverse effects, including dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations, are seen in 53% of patients receiving efavirenz, compared with 25% of those receiving placebo. In most patients, the frequency of these symptoms decreases with time; after 4 weeks of therapy, only 5% to 9% of patients (3% to 5% in the placebo group) have moderate CNS symptoms. However, in the setting of overdose, these symptoms may escalate. According to *Physicians’ Desk Reference*: “Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.” The recommended dosage of efavirenz is 600 mg PO, taken at bedtime to minimize daytime adverse effects. Efavirenz is highly protein-bound and may be associated with increased adverse effects when taken with food because of increased absorption. The time to peak concentration is 3 to 5 hours, but the half-life of efavirenz is 40 to 55 hours. Furthermore, many drug interactions may affect plasma levels of efavirenz, and dosage adjustment may be required. Most interactions result from the metabolism of efavirenz by cytochrome P-450 isoenzymes CYP2B6 and CYP3A4. Other than ritonavir, which may increase plasma efavirenz levels, and tipranavir, which may lower efavirenz levels, our patient was not taking any medications known to interact with efavirenz.

A Canadian study found no significant effect of ritonavir-boosted tipranavir (200 mg/500 mg taken twice daily) on the steady-state pharmacokinetics of efavirenz (600 mg taken once daily). In addition, our patient weighed 95 lb (43 kg) on admission and had cirrhosis. However, since no dosing adjustments are recommended for this patient’s drug regimen (for neither her weight nor her liver disease), she received the standard efavirenz dosage. Although there are no strict guidelines for dosage reduction in the setting of toxicity, many practitioners empirically decrease the dosage of efavirenz—for example, to 400 mg daily in patients who have severe CNS adverse effects, such as psychosis. Despite decreasing our patient’s dosage to 200 mg daily, she was unable to tolerate efavirenz.

There is more recent evidence that there may be an interaction between tenofovir and efavirenz in certain populations. Rotger and colleagues found that most patients receiving both tenofovir and efavirenz, compared with those receiving efavirenz in combination with other NRTIs, had similar plasma efavirenz levels. However, the subset of patients who metabolized efavirenz slowly (those who had 2 copies of CYP2B6 loss/diminished-function alleles) had significantly higher plasma efavirenz levels if they were also receiving tenofovir, compared with those who were receiving efavirenz without tenofovir.

Allavena and colleagues described 9 patients in whom neuropsychiatric symptoms developed after...
their regimen was switched from an efavirenz regimen that did not include tenofovir to one that did. Therefore, there is a suggestion that certain patients may be more susceptible to this drug interaction. Whether the combination of tenofovir with efavirenz played a significant role in our patient's presentation is unclear.

What is clear is that her presentation is consistent with efavirenz toxicity for several reasons. Her plasma efavirenz levels were exceedingly elevated; there are no other reports in the literature, either by case report or in research studies, of plasma efavirenz levels in this range. The causative mechanism is supported by the observation that when efavirenz was discontinued, the patient's CNS symptoms resolved, and when it was restarted, her symptoms returned. In addition, she was able to tolerate her previous medications well once the efavirenz was eliminated from the regimen, confirming that efavirenz was probably causing her symptoms.

It is important to note that this patient did have a previous diagnosis of PML, with resulting encephalomalacia and partial simple seizures. However, this problem had been well controlled with minimal therapy for over a decade, and right-sided symptoms never had been present before the addition of efavirenz. This medication clearly was the \textit{agent provocateur} of her status epilepticus, as evidenced by the absence of new abnormalities on her MRI, the absence of JC virus in her CSF, and the resolution of her symptoms after discontinuation of the efavirenz.

**Is This a Dose-Related Phenomenon?**

Several studies have shown that neuropsychiatric adverse effects of efavirenz correlate with plasma drug levels. A 2001 study by Marzolini and colleagues\textsuperscript{6} found that not only was virological failure more common in those with low levels of efavirenz but also patients with levels higher than 4000 \( \mu \text{g/L} \) were 3 times more likely to experience CNS toxicity.

A 2005 study from Spain looked at the long-term neuropsychiatric adverse effects of efavirenz in 17 patients and found that those with a plasma efavirenz level higher than 2.74 \( \mu \text{g/mL} \) (2740 \( \mu \text{g/L} \)) were 5.7 times more likely to experience CNS toxicity.\textsuperscript{13} These findings are consistent with our case report, given that the patient had a level of nearly 30,000 \( \mu \text{g/L} \) at presentation.

**Which Patient Characteristics Are Associated With High Efavirenz Levels?**

The pharmacogenetics of efavirenz metabolism has been an area of active study. Efavirenz is predominantly metabolized by cytochrome P-450 CYP2B6 and, to some extent, CYP3A4.\textsuperscript{14} Haas and colleagues\textsuperscript{15} studied patients enrolled in the ACTG 5095 and 5097s trials who were receiving efavirenz. They found that the CYP2B6 T/T genotype at position 516 was associated with higher plasma efavirenz levels overall and with increased CNS symptoms in the first week of therapy. This mutation was more common in African Americans.\textsuperscript{15} Haas and colleagues\textsuperscript{16} also looked at this polymorphism (in addition to several others) in the context of ACTG 384 and found again that the CYP2B6 516 G to T mutation resulted in increased plasma exposure to efavirenz; this was true in white, black, and Hispanic patients.

Other studies have looked at the relationship between patient characteristics and efavirenz metabolism. Kappelhoff and colleagues\textsuperscript{17} found that increased bioavailability of efavirenz was associated with Asian ethnicity and with a bilirubin level higher than 1.5 times the upper limit of normal. Burger and colleagues\textsuperscript{2} demonstrated that women and non-white persons were more likely to have elevated levels of efavirenz. African women in particular may be at increased risk for elevated efavirenz levels; a recent study from Zimbabwe found that the prevalence of the CYP2B6 G to T mutation was 49%.\textsuperscript{18} These findings have significant implications for the use of antiretrovirals in the international setting.

Therefore, it appears that select patient populations, such as those with a CYP2B6 516 G to T mutation, women, nonwhite persons, and possibly those with liver disease, may have a greater likelihood of experiencing efavirenz toxicity. A CYP2B6 genotype was performed on our patient using...
real-time polymerase chain reaction assay (Applied Biosystems, Foster City, Calif), and it revealed a T/T genotype at the 516 position. This homozygous G to T mutation indicates that our patient is a slow metabolizer of efavirenz. As a result, in addition to her sex and her liver cirrhosis, our patient has a substantially greater risk for an increased bioavailability of efavirenz by having this CYP2B6 mutation. **When Should We Check an Efavirenz Drug Level?** There are no formal recommendations for therapeutic drug monitoring (TDM) for efavirenz or any other antiretroviral medications. TDM is relevant not only in the setting of toxicity but also in the case of subtherapeutic drug levels, where a patient may be at risk for inadequate virological suppression and potential development of resistance. In a randomized controlled trial of TDM in treatment-naive and treatment-experienced HIV-infected patients, nearly two-thirds of patients had nontarget plasma drug levels at least once during the 48-week study period, and there was a trend toward worse virological response in patients whose drug levels were below target. Of note, efavirenz use was one of the predictors of nontarget concentrations. However, TDM remains controversial, and a major obstacle is the lack of standardization of optimal drug level ranges. In addition, interindividual variability in antiretroviral concentrations may limit the utility of single measurements. Nonetheless, many experts would agree that TDM can be valuable in certain cases. Patients with low body weight (including children), evidence of severe adverse effects, hepatic or renal dysfunction, or unexplained treatment failure may all be candidates for TDM. **Take-Home Point: Could We Have Foreseen or Prevented This Reaction in Our Patient?** Given her female sex, low body weight, and CYP2B6 516 T/T genotype, our patient was at high risk for medication-related adverse effects. Although genotype-based efavirenz dose reduction has been successful in a small number of patients, a preemptive decrease in efavirenz dosage in our patient with advanced AIDS and extensive antiretroviral resistance would have been risky. It could have led to poor virological suppression and additional resistance mutations, and thus, may have delayed immune restoration. However, she was a good candidate for TDM and benefited from this intervention in that it helped identify the cause of her seizures, insomnia, and hallucinations. Fortunately, she has been able to sustain an undetectable HIV RNA level on her current HIV regimen without efavirenz and had complete resolution of her CNS symptoms. HIV practitioners should be aware of the potential adverse effects of efavirenz and its complex metabolism, including a long half-life as well as multiple potential drug interactions. In addition, one should be aware that certain patients carry a CYP2B6 genotype that places them at higher risk for toxicity and that this may be more common in non-white persons, women, and patients with liver disease. Finally, TDM may be useful in select patients, particularly in those with low body weight or hepatic or renal dysfunction, as well as in patients experiencing severe or prolonged adverse effects or unexplained treatment failure. Dr Kwara reports serving as a member of a speaker's bureau for Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported by the authors.

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