Concurrent Use of Efavirenz and Oxcarbazepine May Not Affect Efavirenz Plasma Concentrations

To the Editor—Limited data exist regarding the potential for treatment failure during concurrent use of anticonvulsants and antiretroviral therapy (ART) in individuals with HIV infection [1]. Anticonvulsant medications are commonly used in these patients either for seizure management or expanded indications, such as neuropathic pain and psychiatric disorders. Many anticonvulsants and ART medications are metabolized by the cytochrome P450 enzymes, and clinically significant drug interactions may occur that either increase the toxicity of anticonvulsants or reduce the efficacy of both classes. New anticonvulsant agents, such as oxcarbazepine (Trileptal; Novartis), have improved pharmacokinetics [2] and may have a lower drug interaction potential in patients receiving ART. Here, we present a case of a patient receiving an efavirenz-based regimen who experienced treatment failure shortly after initiating oxcarbazepine. Plasma concentrations of efavirenz were determined before, during, and after concurrent use.

A 28-year-old man with HIV infection (CD4+ cell count, 818 cells/mm3; HIV RNA load, 273,396 copies/mL) whose pretherapy resistance test findings showed wild-type virus initiated therapy with efavirenz, emtricitabine, and tenofovir. The patient had a favorable early viral response, with an HIV RNA load of 561 copies/mL at week 4 and 156 copies/mL at week 8 of ART. However, 4 weeks later, his HIV RNA load increased to 5957 copies/mL. This episode of viral rebound occurred 2 weeks after the patient began treatment with oxcarbazepine for bipolar disorder. Additional testing confirmed treatment failure (HIV RNA load, 60,881 copies/mL), and new drug-resistance mutations at positions 184 M→V, 103 K→N, and 225 P→H were detected. At the time, the patient had noted 100% adherence to his antiretroviral medications.

Stored samples of the patient’s plasma were available, and efavirenz concentrations were determined ~12 h after an unwitnessed dose was administered. Using a Bayesian model, the patient’s efavirenz exposure was estimated and compared with reported population pharmacokinetics using Nonmem software, version V.1 (Globomax) [3, 4]. Efavirenz plasma concentrations were 1.551 µg/mL and 1.898 µg/mL before concurrent use of oxcarbazepine, 1.614 µg/mL during use, and 1.361 µg/mL after use. At all time points, the patient’s level of efavirenz exposure was approximately in the 25th percentile and did not appear to change during oxcarbazepine use. On subsequent questioning, the patient admitted to reduced medication adherence in the weeks before viral rebound.

Treatment failure attributed to drug interactions with anticonvulsants, particularly carbamazepine, has been reported [5], and caution is recommended with concurrent use [6]. However, there may be a lower risk of clinically significant drug interactions with oxcarbazepine and ART. Oxcarbazepine is a weaker inducer of cytochrome P3A4 than carbamazepine [7]. In this case report, coadministration of oxcarbazepine did not reduce efavirenz plasma concentrations. Rather, we believe the patient’s low initial efavirenz exposure and history of intermittent adherence with regard to a regimen with a low genetic barrier to resistance resulted in treatment failure.

To our knowledge, this is the only report of efavirenz plasma concentrations obtained during oxcarbazepine therapy. Many individuals with HIV infection taking ART require treatment with anticonvulsants. Drug interactions may arise and are complex and difficult to predict. Therapeutic drug monitoring of ART should be considered if anticonvulsants are to be coadministered.

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West Nile Virus Encephalitis: Clinical Diagnostic and Prognostic Indicators in Compromised Hosts

To the Editor— I read with interest the article by Penn et al. [1] regarding persistent West Nile virus (WNV) infection in a compromised host. Their report outlines the difficulty in diagnosing WNV meningoencephalitis in a patient with B cell lymphoma in the absence of a WNV serological response.

In compromised hosts with WNV infection and impaired B lymphocyte function, the clinical assessment of the patient may provide clinical clues to the diagnosis and prognosis of WNV encephalitis. The patient described by Penn et al. [1] developed meningoencephalitis during an outbreak of WNV encephalitis. Symptoms consistent with the diagnosis of WNV encephalitis included flaccid paralysis and/or tremor with encephalitis or meningoencephalitis, and the patient’s physicians correctly suspected the diagnosis on day 2 of the patient’s hospitalization [2].

In a patient with encephalitis, either optic neuritis or chorioretinitis, if present, may suggest the possibility of WNV encephalitis [3]; these were not described in this patient [2]. The patient reported had normal head MRI findings, but if the MRI had shown bilateral hyperintensities in the thalamus and/or basal ganglia, the possibility of WNV encephalitis would have been enhanced [4]. Similarly, electroencephalogram findings are not given in the report. Most patients with WNV encephalitis have diffusely abnormal electroencephalogram findings, but some patients with WNV encephalitis have prominent slowing in the anterior regions, which is not commonly seen in other types of viral encephalitis [5].

Serial relative lymphocyte counts are not provided in the report, but the degree and duration of relative lymphopenia has both diagnostic and prognostic importance in WNV encephalitis. If relative lymphopenia (lymphocytes ≤10%) is prolonged and persistent, the diagnosis of WNV encephalitis is likely for otherwise unexplained encephalitis. Furthermore, the more profound and prolonged the relative peripheral lymphocyte count is, the worse the prognosis is. In a patient with encephalitis, the higher the serum ferritin level is, the more likely it is that the patient has WNV encephalitis, compared with other causes of viral encephalitis. Serum ferritin levels may also be useful prognostically. The higher the serum ferritin level (n=240 ng/mL) i.e., levels >500 ng/mL, the more likely it is that there will be neurologic sequelae or a fatal outcome [6, 7].

In conclusion, in patients with WNV encephalitis or meningoencephalitis, an initial low relative lymphocyte count and/or a highly elevated serum ferritin level (≥500 ng/mL) may be helpful in suggesting the diagnosis of WNV encephalitis before serological test results are available. Prolonged and severe relative lymphopenia in patients with WNV encephalitis suggests a complicated course of illness and a guarded prognosis [8]. Serial relative lymphocyte counts and serum ferritin level determinations may be useful diagnostically for patients with WNV meningoencephalitis or encephalitis with a blunted or absent humoral response.

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