BRIEF REPORT

Efavirenz Intoxication Due to Slow Hepatic Metabolism

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We describe a human immunodeficiency virus–positive woman who presented with severe psychosis while she was receiving therapy with efavirenz. Her plasma efavirenz level was excessively high. Genetic investigation showed that she was homozygous for the *CYP2B6* G516T allele, resulting in slow hepatic metabolism. After the dosage of efavirenz was lowered, all neuropsychiatric symptoms subsided.

In the care of HIV-infected patients receiving antiretroviral therapy (ART), clinicians are often confronted with drug toxicities and adverse effects. Most of these toxicities develop despite correct dosing. In cases in which there is significant toxicity, drug treatments are usually withdrawn regardless of the drug serum level. We report the case of a patient who presented at our hospital (Cantonal Hospital of Muensterlingen, Muensterlingen, Switzerland) with sudden and severe neuropsychiatric symptoms during therapy with efavirenz (EFV). To our knowledge, the patient presented with the highest plasma level of EFV ever reported in the literature.

Case report. A 33-year-old, HIV-infected woman who was a native of Thailand was referred to our hospital because of symptoms of acute psychosis. There was no history of previous mental illness. Her husband stated that there had been a 2-week history of confusion, childish behaviour, and verbal aggressiveness. She had stopped taking her antiretroviral agents 5 days before presentation. She stated that, after the cessation of her therapy, she already felt better.

She was known to have been HIV positive since 1994, and her nadir CD4 cell count was 8×10^6 cells/L. She had been treated for cryptococcal meningitis in the past and had already received regimens of several combinations of antiretroviral agents. According to the results of a drug resistance test, she had started a treatment regimen 1 month before admission to the hospital that consisted of lopinavir-ritonavir (400/100 mg twice daily), tenofovir (300 mg once daily), and EFV (600 mg once daily). She was concomitantly receiving fluconazole (400 mg once daily) and trimethoprim-sulfamethoxazole (160/800 mg 3 times per week).

Findings of a complete physical examination and laboratory tests, a lumbar puncture, and MRI of the brain were normal. The CD4 cell count was 86×10^6 cells/L, and the viral load was 36 copies/mL. Almost 1 week after the discontinuation of treatment, all psychiatric symptoms had resolved. Because an interaction between EFV and fluconazole was suspected, the dosage of the antifungal agent was reduced from 400 mg to 200 mg once daily, and the same ART regimen was restarted.

One week later, psychiatric symptoms reappeared. Again, the patient was confused and aggressive, but, this time, she also experienced symptoms of severe depression. Because she wanted to commit suicide with a butcher's knife, she was urgently admitted to a psychiatric ward. Her plasma EFV level was 59.4 mg/L, which is ~30-fold more than the normal limit. One week after ART was discontinued, the patient recovered completely and was discharged from the hospital. The plasma EFV level declined slowly (see figure 1). Subsequently, ART was restarted with a reduced dose of EFV (200 mg once daily). No psychiatric symptoms reappeared. While the patient was receiving EFV at dosages of 200 mg once daily, the plasma drug levels were normal (i.e., in the 50th percentile). After month 6 of therapy, the CD4 cell count was 120×10^6 cells/L, and the viral load was suppressed. Genetic investigation showed that the patient was homozygous for the *CYP2B6* G516T allele.

Discussion. Of patients treated with EFV, 54% develop CNS adverse effects [1–3]. The most common adverse effects are confusion, insomnia, vivid dreams, dizziness, and headaches. These symptoms usually begin shortly after the first days of therapy and generally resolve after 2–4 weeks of therapy. Serious psychiatric effects, including depression, hallucinations, aggression, mania, and psychosis, have been reported less commonly [4–6]. The risk of serious CNS adverse effects associated with use of EFV is greater in patients with mental illness or substance abuse disorders [7]. In patients without such risk factors, high plasma EFV levels are responsible for serious psychiatric complications [8, 9], but the clear relationship between the plasma concentrations, the pharmacokinetics, and the clin-

Received 4 August 2004; accepted 20 September 2004; electronically published 7 January 2005.

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Clinical Infectious Diseases 2005; 40:e22–3

1058-4838/2005/4003-00E2$15.00

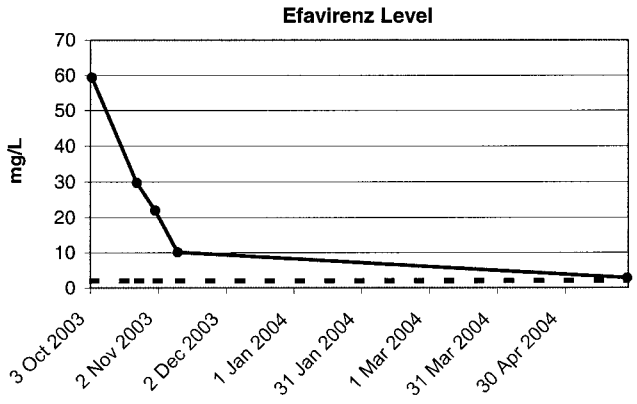

Figure 1. All plasma efavirenz levels were measured 14 h after the last ingestion of the medication. The normal level (i.e., in the 50th percentile) at that time point is 2 mg/L *(dashed line).*

ical CNS adverse effects of EVF is still being investigated. EFV is metabolized primarily by the hepatic cytochrome CYP2B6, a hepatic mixed-function oxidase [10]. Interindividual functional differences in CYP2B6 activity are responsible for different susceptibility to EFV-associated CNS adverse effects [11, 12]. The *CYP2B6* G516T mutation is associated with significantly reduced function of the 2B6 enzyme [13]. Because the patient we describe was homozygous for this mutation, we postulate that slow hepatic metabolism was primarily responsible for the excessively high plasma EFV levels. Furthermore, a drug interaction with fluconazole might have contributed to the accumulation of EFV, because fluconazole has been shown to prolong the elimination half-life of EFV. However, under normal circumstances, no dose adjustment is recommended when EFV and fluconazole are given concomitantly. *CYP2B6* G516T mutations are relatively common among black and Hispanic persons [14], but the prevalence of the mutations among Asian persons is not known at this time, and the mutation may be common.

In conclusion, for persons who develop neuropsychiatric side effects while receiving treatment with EFV, we recommend keeping EFV in the therapeutic armentarium and lowering the dosage, rather than simply stopping treatment with the drug. Additional studies should be performed to evaluate whether genetic investigations should be undertaken before initiation of EFV treatment.

Acknowledgments

We thank the patient we describe, for the opportunity to publish her case.

Potential conflicts of interest. All authors: no conflicts.

References

1. Adkins JC, Noble S. Efavirenz. Drugs **1998**; 56:1055–64.
2. Sustativa [efavirenz] product management monograph [package insert]. Princeton, NJ: Bristol-Myers Squibb; **2002**.
3. Puzantian T. Central nervous system adverse effects with efavirenz: case report and review. Pharmacotherapy **2002**; 22:930–3.
4. Shah MD, Balderson K. A manic episode associated with efavirenz therapy for HIV infection. AIDS **2003**; 17:1713–4.
5. Sabato S, Wesslingh S, Fuller A, Ray J, Mijch A. Efavrienz-induced catatonia. AIDS **2002**; 16:1841–2.
6. Peyriere H, Mauboussin JM, Rouanet I, Fabre J, Reynes J, Hillaire-Buys D. Management of sudden psychiatric disorders related to efavirenz. AIDS **2001**; 15:1323–4.
7. Ruiz NM, Bessen LJ, Manion DJ, et al. The Clinical EFV Development team. Potential adverse experiences associated with EFV in adults [abstract 655]. In: Program and abstracts of the 6th Conference on Retroviruses and Opportunistic Infections (Chicago). Alexandria, VA: Foundation for Retrovirology and Human Health, **1999.**
8. Marzolini C, Telenti A, Decosterd L, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV–1 infected patients. AIDS **2001**; 15: 71–5.
9. Stahle L, Moberg L, Svensson JO, Sonnerborg A. Efavirenz plasma concentrations in HIV-infected patients: inter- and intraindividual variability and clinical effects. Ther Drug Monit **2004**; 26:267–70.
10. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther **2003**; 306:287–300.
11. Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous CYP2B6*6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. Biochem Biophys Res Commun **2004**; 319:1322–6.
12. Haas D, Ribaudo H, Kim R, et al. A common CYP2B6 variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG study NWCS214 [abstract 133]. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (San Francisco). Alexandria, VA: Foundation for Retrovirology and Human Health, **2004**.
13. Rotger M, Colombo S, Furrer HJ, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenetics **2005** (in press).
14. Ribaudo H, Clifford D, Gulick R, et al. Relationship between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response and race: results from ACTG A5095/A5097s [abstract 132]. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (San Francisco). Alexandria, VA: Foundation for Retrovirology and Human Health, **2004**.