Letter to the Editors

Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia

Chris Kenyon,¹ Sipho Mfolozi,² Roland Croxford,³ Robert Colebunders⁵ & Karen Cohen⁴

¹Pieter de Coninckstraat 5, Antwerpen, Belgium, Departments of ²Pathology, ³Medicine, ⁴Pharmacology, University of Cape Town, Cape Town, South Africa and ⁵Head clinical HIV/STD Unit, Institute of Tropical Medicine, University of Antwerp (UA), Antwerp, Belgium

In the setting of closely monitored clinical trials 50% of patients treated with efavirenz develop neuropsychiatric side-effects and 7% experience drowsiness [1]. We present, to our knowledge, the first case of efavirenz-induced coma. We review the clinical, pharmacological and histopathological features of the case and then discuss the possible mechanisms of toxicity.

A 38-year-old Zimbabwean man presented to GF Jooste Hospital, Cape Town, South Africa. He was found to be HIV positive (CD4 count of 58 cells μL^{-1}) and to have biopsy-confirmed HIV associated nephropathy (estimated creatinine clearance 20 ml min^{-1} , Cockcroft-Gault formula). He was commenced on stavudine 15 mg 12 hourly, lamivudine 150 mg daily, nevirapine 200 mg 12 hourly and cotrimoxazole 480 mg daily. A routine blood alanine aminotransaminase done 3 months later was elevated – 561 IU L^{-1} (normal range 5–40). Although he was asymptomatic at this point his nevirapine and cotrimoxazole were stopped. He was found to be positive for hepatitis B surface antigen and had a low body mass index (BMI 17.4 kg m^{-2} and weight 57 kg). He had no problems with his appetite but had insufficient income to feed himself and his two children.

He was given nutritional assistance and, when his transaminases had improved 5 days after stopping the nevirapine, efavirenz 600 mg at night was commenced. When he was seen a week later, he complained of new onset headaches and lightheadedness. A month thereafter, he complained of very vivid and unpleasant dreams in the early hours of the morning and a 'hangover' type sensation when he awoke. He also had a productive cough and his weight had dropped 4 kg. A sputum sample sent at this time came back microscopy negative but culture positive for *Mycobacterium tuberculosis*. On 3/4/09, 2 months after commencement of efavirenz, he was commenced on rifampicin, isoniazid, pyrazinamide and ethambutol. At this stage his liver function tests had completely normalized.

He returned on 26/4/09 complaining of mental slowing and a sensation of being confused when he woke up. These symptoms improved somewhat through the course of the day. On examination he was found to be slow and apathetic. He was slightly ataxic but had no other focal neurological abnormalities. He scored 6/12 on the International HIV/AIDS Dementia Scale (memory 2, fine motor 4, psychomotor 0). An uncontrasted CT scan of his brain showed mild generalized cerebral atrophy.

On 5/5/09 he came to hospital complaining of being sleepy all the time. He was still orientated but took a long time to answer questions. Three days later, he was brought back to hospital in an extremely drowsy state. He still answered questions and obeyed commands but there was a 3 s gap between instruction and response. His pupils reacted to light but there was a considerable delay before constricting. He was too unsteady to be able to walk. Examination of his cerebrospinal fluid was normal – Cryptococcus Latex Antigen Test negative, VDRL negative, negative cultures for bacteria, fungi and mycobacteria. His calcium, vitamin B12, glucose, TSH and liver function tests were normal and his estimated creatinine clearance was 23 ml min^{-1} . The efavirenz and isoniazid were changed to nevirapine and ofloxacin respectively and pyridoxine (100 mg day^{-1}) was administered.

Despite these interventions he became more and more drowsy. By 14/05/09, he was unable to swallow normally and his Glasgow Coma Scale had dropped to 8/15. His pupillary light reflexes, though present and equal, were markedly sluggish. He was therefore transported to a tertiary hospital but aspirated and died the following day.

Post-mortem examination revealed extensive aspiration pneumonia. His brain showed no evidence of a meningo-encephalitis but there were features of an extensive axonal vacuolopathy, including in his cerebellum. The central white matter displayed widespread but variable, coarse vacuolation, with many individual spaces being clearly rimmed with myelin, and containing displaced but

Figure 1

(A) Central white matter showing diffuse vacuolation. (B) Detail showing vacuoles rimmed by myelin, and containing displaced axons (arrows). Luxol fast blue/H&E ×100 & 200

normal-appearing axons (see Figure 1). This process was most marked within the hila of the dentate nuclei, where there was occasional coalescence together with possible spheroid formation. Pigmented macrophages were occasionally present within the perivascular spaces. Immunoreactivity for HSV-1, HSV-2, VZV, HIV and CMV were negative.

The efavirenz plasma concentration 5 days after stopping the efavirenz, was 13.7 mg l⁻¹ (recommended range for efavirenz trough concentrations is 1–4 mg l⁻¹) [2].

Efavirenz-induced hypersomnolence leading to coma and death has not previously been reported. We were, however, unable to find alternative causes. A large number of medications and toxins have been noted to result in a vacuolar axonopathy [3, 4]. This is thought to be secondary to a toxic effect on mitochondria. Efavirenz has been shown to result in mitochondriopathy but thus far this has been found to occur mainly in hepatocytes [5]. The nucleoside reverse transcriptase inhibitors (NRTI), and stavudine in particular, have been associated with a range of neurological side effects, most plausibly due to mitochondrial toxicity. Although this may have contributed to the pathology in this case we felt it was unlikely to be the primary aetiology for a number of reasons. Firstly, stavudine has not been linked to toxicity in the central nervous system (CNS). Secondly, the patient had no other clinical features of a NRTI-induced mitochondriopathy. Thirdly, the temporal relationship between the onset of symptoms fitted closely with the timing of the switch to efavirenz. Finally the drug concentrations of efavirenz were markedly elevated, a finding which has been found to correlate with increased CNS side effects.

The incidence of neuropsychiatric side effects on efavirenz is correlated with plasma concentrations [2]. Elevated concentrations are in turn correlated with amongst other factors, the cytochrome P450 isoenzyme 2B6 G > T polymorphism [6]. A high proportion of Southern Africans have this polymorphism. In one study 38% were found to be G/T heterozygotes and 13% T/T homozygotes, compared with 3% T/T homozygotes found in Caucasian populations [7]. Patients in Southern Africa and other regions where slow metabolizing polymorphisms are common, may therefore be at increased risk of severe neuropsychiatric side effects of efavirenz. There are a number of drug interactions which may have influenced his efavirenz concentrations. These include rifampicin which induces the expression of cytochrome P450 isoenzyme 2B6 (CYP 2B6) which metabolizes efavirenz and may result in lower efavirenz concentrations [7, 8]. Isoniazid is a reversible inhibitor of CYP3A4 and CYP2C19. Since efavirenz is a metabolic substrate of CYP2B6, concomitant isoniazid may increase efavirenz concentrations [9, 10].

Since, this patient's tragic demise we have seen a further three patients with efavirenz-induced extreme drowsiness (and efavirenz trough concentrations up to 16 times above the upper limit of recommended range) who all responded well to dose adjustment or drug switching. Dose adjustment in patients with elevated concentrations has been shown to be safe [11]. We would therefore recommend that clinicians be aware of this side effect, measure efavirenz concentrations when patients manifest severe and prolonged neuropsychiatric side effects and

reduce the dose where concentrations are above the recommended trough range.

Competing Interests

There are no competing interests to declare.

REFERENCES

- 1 Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. *AIDS Behav* 2011; 15: 1803–18.
- 2 Marzolini C, Telenti A, Decosterd LA, 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.
- 3 Tormoehlen LM. Toxic leukoencephalopathies. *Neurol Clin* 2011; 29: 591–605.
- 4 Kass-Hout T, Kass-Hout O, Darkhabani MZ, Mokin M, Mehta B, Radovic V. 'Chasing the dragon'—heroin-associated spongiform leukoencephalopathy. *J Med Toxicol.* 2011; 7: 240–2.
- 5 Blas-García A, Apostolova N, Ballesteros D, Monleón D, Morales JM, Rocha M, Victor VM, Esplugues JV. Inhibition of mitochondrial function by efavirenz increases lipid content in hepatic cells. *Hepatology* 2010; 52: 115–25.
- 6 Rakhmanina NY, van den Anker JN. Efavirenz in the therapy of HIV infection. *Expert Opin Drug Metab Toxicol* 2010; 6: 95–103.
- 7 Cohen K, Grant A, Dandara C, McIlleron H, Pemba L, Fielding K, Charalombous S, Churchyard G, Smith P, Maartens G. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther* 2009; 14: 687–95.
- 8 López-cortés LF, Ruiz-Valderas R, Viciano P, Alarcón-González A, Gómez-Mateos J, León-Jimenez E, Sarasanacenta M, López-Pua Y, Pachón J. Pharmacokinetic interactions between efavirenz and rifampin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002; 41: 681–90.
- 9 Wen X, Wang J-S, Neuvonen PJ, Backman JT. Isoniazid is a mechanism-based inhibitor of cytochrome P450 1A2, 2A6, 2C19, and 3A4 isoforms in human liver microsomes. *Eur J Clin Pharmacol* 2002; 57: 799–804.
- 10 Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) by isoniazid: potent inhibition of CYP2C19 and CYP3A. *Antimicrob Agents Chemother* 2001; 45: 382–92.
- 11 Gatanaga H, Hayashida T, Tsuchiya K, Yoshino M, Kuwahara T, Tsukada H, Fujimoto K, Sato I, Ueda M, Horiba M, Hamaguchi M, Yamamoto M, Takata N, Kimura A, Koike T, Gejyo F, Matsushita S, Shirasaka T, Kimura S, Oka S. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis* 2007; 45: 1230–7.

RECEIVED

2 February 2012

ACCEPTED

10 April 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

18 April 2012

CORRESPONDENCE

Dr Chris Kenyon, Pieter de Coninckstraat 5, Antwerpen 2600, Belgium.
Tel.: +32 4 8978 3329
Fax: +32 (0) 3216 1431
E-mail: chriskenyon0@gmail.com