Published by iambr.info/AMBR

Open Access Case Report

Long term adverse drug reaction to Efavirenz in a HIV infected adolescent

Gbaja-Biamila TA[1], David AN[1], Herbertson EC[1], Ohwodo H[1], Ezeobi P[1], Ohihoin AG[1], Ezechi OC[1]

To cite: Gbaja-Biamila TA, David AN, Herbertson EC, Ohwodo H, Ezeobi P, Ohihoin AG, Ezechi OC. Long term adverse drug reaction to Efavirenz in a HIV infected adolescent. *Arch Med Biomed Res.* 2015;2(4):142-5. doi: 10.4314/ambr.v2i4.5

Publication history
Received: July 26, 2015
Revised: August 21, 2015
Accepted: August 31, 2015

CrossRef Link
http://dx.doi.org/10.4314/ambr.v2i4.5

Correspondence to
Herbertson Ebiere;
ebiereh@yahoo.com

ABSTRACT

Efavirenz is one of the medications used in combined antiretroviral therapy (ART) for the management of HIV infection in adolescents. Various central nervous system adverse reactions have been reported in patients commencing antiretroviral therapy with a regimen containing Efavirenz. These reactions tend to be acute, commonly occurring in the first six months of therapy. Adverse reactions following long term use of Efavirenz for ART is rare among adults and rarer still among children and adolescents. There is only one published case of serious adverse reaction to Efavirenz in an adolescent after long-term use. The case of a male HIV Positive Nigerian patient aged 13 years. He presented with five-day history of Difficulty sleeping, abnormal dreams, inability to concentrate, restlessness, irrational behavior and long-term memory loss. There was no previous history of psychiatric illness and no suggestive social or family history. Patient was on Efavirenz containing regimen about 6.5 years till presentation with adverse reaction mainly affecting behavior, thought processes and memory. After discontinuing Efavirenz and replacing with Nevirapine in his combined ART regimen, all neuropsychiatric manifestations ceased .He regained his memory, no longer had bad dreams or demonstrated any irrational behavior or attitude. Physicians who are involved in the care of HIV infected patients need to be aware of the possibility of adverse Drug reactions occurring in patients who have been on antiretroviral drugs for years. This possibility should not be excluded from possible differential diagnosis.

KEY WORDS: ***Adolescent; Efavirenz; HIV Infection; Reactions; Adverse drug; Psychomotor Agitation; Long term***

RATIONALE FOR ANTI-RETROVIRAL THERAPY (ART)

Antiretroviral (ARV) drugs are the main stay of treatment for adults and children infected with Human immunodeficiency Virus (HIV). Currently there has been an increase in access to highly active antiretroviral therapy and this has made the management of drug toxicities an increasingly vital part of human immunodeficiency virus (HIV) care in developing countries[1]. The treatment is for life and with children they will continue to take the medications for the rest of their lives except if a cure is found for HIV. The intake of these drugs can sometimes lead to unwanted effects to the body, which could be harmful, or life threatening. These effects usually are seen in the

early stage of drug intake. It has been observed that the possibility of developing an adverse drug reaction is highest in the first six months of initiating antiretroviral therapy[2]. The early occurrence of ADRs is said to be an expression of a mechanism of intrinsic intolerance rather than of a time-dependent toxic accumulation process[3].

Much is not known about long-term effects of ARTs but there are on-going researches that may provide insights into some ADRs of ARV[4]. This long term effects of ART would be better studied in Children and those children that acquired the infection from their mothers and were started on ART as infants and are now growing into adulthood, as such the effects of these drugs can be studied in these group of children. It is in this view that we observed neurological ADRs in a child who had been on Efavirenz for about six years and six months. Currently information on long-term central nervous system (CNS) toxicity associated with Efavirenz therapy is scarce, and risk factors remain largely unknown[5].

CASE DETAILS AND DEMOGRAPHIC INFORMATION

The patient first presented at the outpatient clinic of Nigerian Institute of Medical Research on the twelfth of January two thousand and seven (12/01/07). He was six years old when he first presented at the clinic. Western Blot testing on the sixth of January two thousand and seven (16/01/2007) confirmed that he was HIV-1 positive.

The patient is male aged 13 years, born on the twenty-six of May two thousand (26/05/2000). He was the elder of two children from the same parents. He and his only sibling were infected with HIV. Two months before presenting at our clinic his mother died. His father who was about 43 years then was a businessman. He lives with his father and brother. Patient is in Secondary school.

Patient was started on ART, NVP/AZT/3TC on the twenty fourth of April two thousand and seven (24/04/2007). As at the time our center was receiving drugs from the National ARV program as well as the President's Emergency Plan for AIDS Relief (PEPFAR). Programs in sub-Saharan Africa attain treatment outcomes similar to those in North America and Europe; although progress is slow in some areas it is essential to improve the care of HIV-infected children in sub-Saharan Africa[6].

On the fifth of June two thousand and seven (05/06/2007) patient was commenced on Tuberculosis (TB) therapy after a diagnosis of Pulmonary Tuberculosis was made. Nevirapine (NVP) was then stopped and was commenced on (Efavirenz) EFV. EFV started on the second of July two thousand and seven (02/07/2007) two weeks after NVP containing regimen was stopped. The TB therapy given was according to National Guidelines and therefore contained Rifampicin, hence the need to substitute Efavirenz for Nevirapine in his ART regimen. Rifampicin is known to induce the metabolism Nevirapine and significantly reduce its usefulness for concomitant ART. He was treated for 8 months and cured of TB. All TB drugs were then discontinued. He had been stable thereafter till he developed ADR to EFV on the eighteenth of January two thousand of fourteen. Presence of Opportunistic infections like Tuberculosis has been said to be possible risk factors to the development of ADR[7].

The dose of his ARV was adjusted according to weight taken at the clinic during clinic visits. ARV needs to be carefully adjusted in children for this reason. Therapeutic drug monitoring is strongly recommended to meet Efavirenz plasma levels within the therapeutic range[8]. The patient's dose adjustment is according to the international guidelines regulating ART dosage to body weight.

SYMPTOMS AND LABORATORY TEST OUTCOMES

On the twenty third of January two thousand and fourteen (23/01/2014), patient presented to the clinic with psychiatric symptoms, difficulty concentration, difficulty sleeping, abnormal dreams, restlessness and long term memory loss. These symptoms were observed in his school and father was told that his son had changed in his behaviour.

Patient's father reported that the symptoms started five days before he presented to the clinic. EFV was stopped and patient was placed on NVP containing regimen. He came back to the clinic two week after with complete remission of all symptoms. A month after patient has been stable on the NVP combination with AZT and 3TC.

He is presently been considered for second line treatment of ART as his CD4 count has dropped from one thousand one hundred and ninety-two (1192 cell/mm3) in a test done on the eighteenth of April two thousand and twelve (18/04/2012) to seven hundred and ninety four (794) on eighteenth of April two thousand and thirteen (17/04/13), and then to 593 on the twenty eighth of October two thousand and thirteen (28/10/2013).

Father claims that the patient has been very adherent to the ARV drugs. Data has shown that insufficient plasma concentrations occur for some children even though Efavirenz dosing is according to recommendations[9]. Patient may have developed resistance to this regimen so change of ART was needed, though it is also possible that the adverse effect might have impacted on adherence. Consequently, this has shown that there is an urgent need for more prospectively collected data on the use of Efavirenz in HIV-infected children[10]. Presently patient is reported to have no ADR and has been stable.

DISCUSSION PERSPECTIVES ON EFAVIRENZ THERAPY IN HIV-INFECTED PATIENTS

Few reports exist on long term Efavirenz associated neuropsychosis. Some of such reports carried out further studies to determine other associated causative factors. Allavena *et al* suggested that combining Tenofovir with Efavirenz was a predisposing factor to occurrence of Efavirenz associated neuropsychosis[11]. Their work was not able to determine the mechanism of Tenofovir interaction with Efavirenz. This case report was not on Tenofovir but instead, was on Zidovudine, Lamivudine and Efavirenz. Lowenhaupt *et a*l reported a case of psychosis in a 12-year-old white girl with increased serum concentration of Efavirenz, which was attributed to CCYP2B6-G516T polymorphism[12]. Gutierrez *et al* carried out a longitudinal study of 18 months duration to determine the effect of serum concentration of Efavirenz on long term Efavirenz toxicity[5]. The study observed that in patients with HIV infection receiving long-term therapy with efavirenz containing antiretroviral regimens, CNS toxicity was linked with Efavirenz plasma levels that higher the plasma levels the greater the Patients risk of experiencing neuropsychiatric adverse events. This was also observed in another study where neuropsychiatric adverse events were said to be common with patients on Efavirenz[9]. Our centre being a resource limited setting unfortunately has neither the facility to check the plasma level of the drugs nor the facilities to test for polymorphisms. Indeed certain undetermined occurrences in the adolescent's lifestyle may have led to increase systemic Efavirenz concentrations, which resulted in the neuropsychosis reported.

CONCLUSION

CNS toxicity in children after long-term (>3 years) use of EFV has not been reported. This case study reports a case of CNS adverse event occurring after more than 6 years on Efavirenz based antiretroviral therapy. This report can alert physicians who are involved in the care of HIV infected patients in resource limited settings to the possibility of adverse drug reactions occurring in patients who have been on Efavirenz based-antiretroviral therapy for many years that should not be excluded from possible differential diagnosis.

Author affiliations
[1]Clinical Sciences Division, Nigerian Institute of Medical Research, Yaba, Lagos, Nigeria

REFERENCES

1. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis*. 2007;45(8):1093-101.
2. Duval X, Journot V, Leport C, Chêne G, Dupon M, Cuzin L, et al. Incidence of and risk factors for adverse drug reactions in a prospective cohort of HIV-infected adults initiating protease inhibitor-containing therapy. *Clin Infect Dis*. 2004;39(2):248-55.
3. Eluwa GI, Badru T, Agu KA, Akpoigbe KJ, Chabikuli O, Hamelmann C. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clin Pharmacol*. 2012;12:7.
4. World health Organization, Health Technology and Pharmaceuticals, Medicines Policy and Standards. Pharmacovigilance for antiretrovirals in resource-poor countries. Geneva: WHO. 2007:1-18.
5. Gutiérrez F, Navarro A, Padilla S, Antón R, Masiá M, Borrás J, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. 2005;41(11):1648-53.
6. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis*. 2008;8(8):477-89.
7. Modayil RR, Harugeri A, Parthasarathi G, Ramesh M, Prasad R, Naik V, et al. Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India. *Pharmacoepidemiol Drug Saf*. 2010;19(3):247-55.
8. von Hentig N, Koenigs C, Elanjikal S, Linde R, Dunsch D, Kreuz W, et al. Need for therapeutic drug monitoring in HIV-1 infected children receiving efavirenz doses according to international guidelines. *Eur J Med Res*. 2006;11(9):377-80.
9. Nelson M, Stellbrink HJ, Podzamczer D, Banhegyi D, Gazzard B, Hill A, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS. 2011;25(3):335-40.
10. Wintergerst U, Hoffmann F, Jansson A, Notheis G, Huss K, Kurowski M, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother*. 2008;61(6):1336-9.
11. Allavena C, Le Moal G, Michau C, Chiffoleau A, Raffi F. Neuropsychiatric adverse events after switching from an antiretroviral regimen containing efavirenz without tenofovir to an efavirenz regimen containing tenofovir: a report of nine cases. *Antivir Ther*. 2006;11(2):263-5..
12. Lowenhaupt EA, Matson K, Qureishi B, Saitoh A, Pugatch D. Psychosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. *Clin Infect Dis*. 2007;45(10):128-30.