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Central Nervous System Effect of Efavirenz at Wangaya Hospital 2017 - 2020

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Abstract: ***Background: Efavirenz is commonly used of NNRTI that produces its antiretroviral activity by binding directly to the enzyme reverse transcriptase, thus inhibiting replication of the virus.One reason for that, efavirenz to cross the blood-brain barrier and can cause central nervous system (CNS) adverse effect. In addition, we have discussed the efavirenz CNS symptoms include dizziness, headache, insomnia, anxiety, vivid or abnormal dreams. Methodology: we conducted descriptive use medical record data from patient living with HIV/AIDS (PLWHA) with efavirenz theraphy at Wangaya Regional General Hospital in Bali, Indonesia during 2017-2020. We excluded PLWHA under age <18, pregnant women, patients with documented CNS illness prior to starting EFV and those who did not give consent to participate. Results: A total of 682 samples are analyzed, 456 (66.9%) samples with neuropsychiatric symptoms and 226 (33.1%) samples without neuropsychiatric symptoms. Conclusion: In Conclusion, this study has shown that neuropsychiatric adverse effect event associated with efavirenz based ART had onset for the symptoms.***

Keywords: efavirenz, CNS, ART, descriptive

1. Introduction

HIV cannot be cured. The introduction of several drugs used for management of HIV are entry inhibitors, fusion inhibitors, integrase inhibitors, protease inhibitors and reverse transcriptase inhibitors (nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors).[1]Antiretroviral theraphy (ART) regimens have the ability to reduce patient human immunodeficiency virus (HIV) load to undetectable levels and decreasing HIV-related opportunistic infections by increasing their CD4 T-lymphocyte counts.[2-4]Antiretroviral contains of two nucleoside reverse transcriptase inhibitors (NRTIs) as a backbone and one non-nucleoside reverse transcriptase inhibitors (NNRTI) is maintained as the preferred first-line treatment regimens in adults because of its high viral suppression.[5]

Efavirenz is commonly used of NNRTI that produces its antiretroviral activity by binding directly to the enzyme reverse transcriptase, thus inhibiting replication of the virus.[6]One reason for that, efavirenz to cross the blood-brain barrier and can cause central nervous system (CNS) adverse effect.[7]Symptoms of CNS toxicity which include dizziness, irritability, headache, diminished concentration, euphoria, vertigo and depression are usually mild to moderate and relatively well tolerated. Sleep disturbance (somnolence, insomnia, and vivid or abnormal dreams) is particulary characteristic of efavirenz. Approximately 2% of subjects report more serious neurological effects, including delusion, paranoia, depersonalization, hallucinations, anxiety, aggressive behaviour, abnormal thinking, mania and severe depression. [8,9,10]

The goal of this study, we have discussed the efavirenz CNS symptoms include dizziness, headache, insomnia, anxiety, vivid or abnormal dreams at Wangaya Regional General Hospital in Denpasar, Bali was conducted.

2. Methodology

Study Population and Design

A hospital-based descriptive design was conducted using medical record data from patient living with HIV/AIDS (PLWHA) at Wangaya Regional General Hospital in Bali, Indonesia during 2017-2020. Study participants were adults (age ≥ 18 years) PLWHA received guidelines of treatment are : tenofovir + lamivudine + efavirenz/nevirapine (TDF+3TC+EFV/NVP) or zidovudine + lamivudine + nevirapine/efavirenz (AZT+3TC+NVP/EFV). We excluded PLWHA under age <18, pregnant women, patients with documented CNS illness prior to starting EFV and those who did not give consent to participate. From the previous study, patients therapy with efavirenz have CNS adverse effect was conducted.

3. Results

Characteristics of the Study samples

This study's goal is to assess the neuropsychiatric symptoms of efavirenz usage at Wangaya Hospital, Denpasar, Bali, Indonesia in 2017 – 2020. In this study, a total of 682 samples are analyzed, 456 (66.9%) samples with neuropsychiatric symptoms and 226 (33.1%) samples without neuropsychiatric symptoms. In Table 1, we found that 356 (52.2%) are male, 326 (47.8%) are female, 106 (15.5%) are in group age 18 – 25, 405 (49.4%) are in group age 26 – 40, 111 (16.3%) are in group age 41 – 50, and 60 (8.8%) are in group age >50 years old.

In this study, authors only follow up 5 neuropsychiatric symptoms after efavirenz usage, headache, dizziness, abnormal dreams, insomnia, and anxiety. There are 163 (23.9%) participants being abnormal dreams, 160 (23.5%) participants being dizziness, 134 (19.6%) participants being headache, 107 (15.7%) participants being anxiety, and 65 (9.5%) participants being insomnia. Neuropsychiatric symptoms appear in different onset. In a total of 456

participants, there are 294 (64.4%) participants in a week, and 162 (35.6%) participants in a week- a month.

Table 1: Characteristics of Study Samples (n: 682)

Variable	n (%)
Non-Neuropsychiatric Symptoms	226 (33.1)
Neuropsychiatric symptoms	
• Abnormal dreams	163 (23.9)
• Dizziness	160 (23.5)
• Headache	134 (19.6)
• Anxiety	107 (15.7)
• Insomnia	65 (9.5)
Sex	
• Male	356 (52.2)
Female	326 (47.8)
Age	
• 18 – 25	106 (15.5)
• >25–40	405 (49.4)
• >40–50	111 (16.3)
• >50	60 (8.8)
Onset	
• <1 week	294 (64.4)
1 week- 4 weeks	162 (35.6)

4. Discussion

We have explored the CNS adverse effects have been commonly associated with efavirenz. In clinical trials, 54% of patients taking efavirenz reported CNS adverse effects compared with 27% of patients not taking efavirenz. Furthermore, 2.6% of patients reportedly discontinued treatment due to CNS effects.[11]Efavirenz had long life half life of 40-55 hours and mostly (90%) metabolized in the liver through a process involving in the cytochrome P450 system and the generation of metabolites that are inactive in terms of antiviral activity. The specific isoform CYP450 2B6 (CYP2B6) is responsible for the hydroxylation of efavirenz to 8-hydroxyefavirenz the most important of its metabolites, which may be implicated in its CNS toxicity.[12,13]The variations in the general pharmacokinetics of efavirenz described for some differences in clinical outcomes, with polymorphisms in CYP2B6 being a particulary relevant genetic determinant. The most significant allelic variant of CYP2B6 is the single point mutation mapped to exon 4 at position 516, which changes G to T. There is clear correlation between CYP2B6 and high plasma concentration or longer plasma half-life of efavirenz.[14]In this study, a total of 682 samples are analyzed, 456 (66.9%) samples with neuropsychiatric symptoms and 226 (33.1%) samples without neuropsychiatric symptoms.

The study have been describing levels of efavirenz and its metabolites in patients randomized to 600 mg and 400 mg of efavirenz daily showed a mean plasma concentration of 5.4 μM 8-hydroxyefavirenz in the patients treated with 600 mg of efavirenz and a surprisingly similar level (5.6 μM) with 400 mg of efavirenz.[15]The another study of efavirenz induced CYP enzymes, multiple doses of 200-400 mg per day for 10 days resulted in lower than predicted of extent accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single-dose half-life of 52-76 hours).[16]

Most studies reporting efavirenz neuropsychiatric toxicity have been based on short term follow up of few weeks but a cross sectional study by Fumaz et al. 60 patients who had been on efavirenz for a mean time of 91.1± 39.5 weeks found that mild clinical tolerable neuropsychiatric disorder persisted.[17]Literature shows that neuropsychiatric symptoms that develop after initiation of efavirenz theraphy occur mainly during first month of efavirenz theraphy.[18] The finding of study Sabina Mugusi, et al. shows that of manifestations occurs within the first week of efavirenz initiation.[19]The finding is consistent with other studies where the most severe toxicity sypmtoms of efavirenz treatment have been reported within first 2-4 weeks after treatment initiation and symptoms generally cease after 6-8 weeks.[20,21]

CNS toxicity has been reported in 40-60% and psychiatric events in 25-40% of patients efavirez making these drug most frequent side effect which include dizziness, irritability, headache, diminished concentration, euphoria, vertigo, and depression are usually mild to moderate and relatively well tolerated. Sleep disturbance (somnolence, insomnia and vivid or nightmares) is particularly characteristic of efavirenz. Approximately 2% of subjects report more severe neurological effects including delusion, paranoia, depersonalization, hallucinations, anxiety, aggressive behaviour, abnormal thinking, mania and severe depression.[14]The 2014 Guidelines warn that efavirenz persistent CNS effect such as abnormal dreams, depression or mental confussion and that these side-effects are more likely to occur in patients with current or previous depression or other mental disorder or if the efavirenz is taken during the day.[22]In this study, authors only follow up 5 neuropsychiatric symptoms after efavirenz usage, headache, dizziness, abnormal dreams, insomnia, and anxiety. There are 163 (23.9%) participants being abnormal dreams, 160 (23.5%) participants being dizziness, 134 (19.6%) participants being headache, 107 (15.7%) participants being anxiety, and 65 (9.5%) participants being insomnia.

5. Conclusion

In conclusion, this study has shown that neuropsychiatric adverse effect events associated with efavirenz based ART. Those adverse effect events appear in several onset after ART.

6. Limitations of Study

The limitations of this study included its small sample size. This study conducted at Wangaya Regional General Hospital in Denpasar, Bali, Indonesia during 2017-2020. Since this is a hospital-based study which only included PLWHA who attended Wangaya Regional General Hospital in Denpasar, Bali, Indonesia during the study period, so the result cannot be generalized to all HIV-infected patients in Bali.

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8. Author Contribution

All author made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; took part indrafting the article or revising it critically for important intellectual content, gave final approval of the vision to be published, and agree to be accountable for all aspects of the work.

9. Disclosure

The authors report no conflicts of interest in this work.

References

[1] Avert: AVERTing HIV and AIDS. http://www.avert.org/hiv-and-aids-treatment-care.htm (accessed 13 February 2015).
[2] Masenyetse LJ, Manda SO, Mwambi HG. An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. AIDS Res Ther. 2015;12(1):6. doi:10.1186/ s12981-015-0044-0
[3] Agu K, Ochei U, Oparah A, Onoh O. Treatment outcomes in patients receiving combination antiretroviral therapy in Central Hospital, Benin City, Nigeria. Trop J Pharm Res. 2010;9(1). doi:10.4314/tjpr. v9i1.52028.
[4] Agu KA, King RC, Isah MA, and Iyaji PG. Medication adherence and risk factors for non-adherence among patients taking highly active antiretroviral therapy. West Afr J Pharm. 2011;22:1.
[5] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - Second edition Geneva, Switzerland. 2016 [updated June 2016; cited July 23, 2020]. Available from: https://www.who.int/hiv/pub/arv/arv-2016/ en/. Accessed September 16, 2020.
[6] Cavalcante GIT, Capistrano VLM, Cavalcante FSD, et al. Implications of efavirenz for neuropsychiatry: A review. Int J Neurosci 2010;120(12):739-745. [http://dx.doi.org/10.3109/ 00207454.2010.520541]
[7] Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV. Efavirenz and the CNS: what we already know and questions that need to be answered. J Antimicrob Chemother. 2015;70 (10):2693–2708. doi:10.1093/jac/dkv183
[8] Gutie´rrez-Valencia A, Viciana P, Palacios R et al. Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Ann Intern Med 2009; 151: 149 – 56.
[9] Scourfield A, Zheng J, Chinthapalli S et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. AIDS 2012; 26: 1399–401.
[10] Leutscher PD, Stecher C, Storgaard Metal. Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects. Scand J Infect Dis 2013; 45: 645–51.
[11] Ruiz NM, Bessen LJ, Manion DJ, for the Efavirenz Clinical Development Team. Potential adverse experiences associated with efavirenz (Sustiva) in adults. Presented at the 6th conference on retroviruses and opportunistic infections. Chicago, IL, February 1-5, 1999.
[12] Piscitelli SC. Space out drug discontinuations prior to 'drug holiday'? Medscape. 2000. http:// www.medscape.com/viewarticle/413306 (accessed 1 September 2014).
[13] Ward BA, Gorski CJ, Jones DR et al. The cytochrome P450 2B6 is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as substrate marker of 2B6 catalytic activity. J Pharmacol Exp Ther 2003; 306: 287–300.
[14] Uriel S, Anthony TP, Courtney VF, Andrew O, Angela FC, et al. Impact of efavirenz pharmacokinetics and pharmacogenomics on neuropsychological performance in older HIV-infected patients. Journal antimicrobial theraphy 2017;72:200-204
[15] Winston A, Amin J, Clarke A et al. Cerebrospinal fluid exposure of efa- virenz and its major metabolites when dosed at 400 mg and 600 mg once daily: a randomized controlled trial. Clin Infect Dis 2015; 60: 1026 – 32.
[16] Wande AN. Handbook of Pharmaceutical excipients, 2th ed. American Pharmaceutical Association. 1994
[17] Fumaz C.R., Muñoz-Moreno J.A., Moltó J. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. J Acquir Immune Defic Syndr. 2005;38:560–565.
[18] Lochet P, Peyriere H, Lotthe A, Mauboussin JM, Delmas B, Reynes J. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med. 2003;4(1):62–66. doi: 10.1046/j.1468-1293.2003.00136.x.
[19] Sabina M, Eliford N, Mohammad J, Ferdinand M, Omary M, et al. Neuropsychiatric manifestations among HIV-1 infected African patients receiving efavirenz-based cART with or without tuberculosis treatment containing rifampicin. European Journal of Clinical Pharmacology. 2018;74:1405-1415.
[20] Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf. 2007;6:147–54.
[21] Cespedes MS, Aberg JA. Neuropsychiatric complications of antiretroviral therapy. Drug Saf. 2006;29:865–74.
[22] National Consolidated Guidelines for the Prevention of Mother-to-child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2014. Pretoria: National Department of Health, 2014.