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EFFECTS OF CHRONIC ADMINISTRATION OF EFAVIRENZ ON THE BRAIN AND INFERIOR COLLICULUS WEIGHTS OF ADULT WISTAR RATS

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SUMMARY:

The effects of chronic administration of Efavirenz commonly used as part of highly active antiretroviral therapy (HAART) for the treatment of Human Immunodeficiency Virus (HIV) type-1 on the weight of the brain and inferior colliculus of adult wistar rats was carefully studied. The rats of both sexes (n=16), with an average weight of 200g were randomly assigned into treatment (n=8) and control (n=8) groups.

The rats in the treatment group received 600 mg/70 kg body weight of Efavirenz dissolved in distilled water daily for 30 days (thirty days) through the orogastric tube. The control group received equal volume of distilled water daily for 30 days through the same route. The rats were fed with grower's mash obtained from Edo Feeds and Flour Mill Limited, Ewu, Edo state, Nigeria and given water liberally. The rats were sacrificed by cervical dislocation method on the thirty-first day of the experiment and the brains were carefully dissected out, dried, weighed and recorded using the Mettler Toledo weighing balance.

The findings indicate that there was a significant decrease ($P < 0.05$) in the dry brain weight and an increase in the relative dry brain weight of the treatment group as compared with the control group in this experiment. There was also a significant increase ($P < 0.05$) in the weight of the dry inferior colliculus per total dry brain weight in the treatment group when compared with the control group. However, the relative dry inferior colliculus weight was significantly higher ($P < 0.05$) in the treatment group also than that of the control group in this experiment

KEY WORDS: Efavirenz. Wistar Rats. Brain. Inferior Colliculus.

RESUMEN: EFECTOS DE LA ADMINISTRACIÓN CRÓNICA DE EFAVIRENZ EN EL PESO DEL CEREBRO Y COLÍCULIO INFERIOR DE RATAS WISTAR ADULTAS.

Los efectos de la administración crónica de Efavirenz comúnmente utilizados como parte de la terapia antirretroviral altamente activa (HAART) para el tratamiento del Virus de Inmunodeficiencia Humana (VIH) tipo-1 en el peso del cerebro y colículo inferior de adultos ratas Wistar han sido cuidadosamente estudiados. Ratas de ambos sexos (n = 16), con un peso promedio de 200 g fueron asignadas aleatoriamente a dos grupos, uno de tratamiento (n = 8) y otro control (n = 8).

Las ratas del grupo de tratamiento recibieron diariamente 600 mg/70 kg de peso de Efavirenz disuelto en agua destilada durante 30 días a través de una sonda gástrica. El grupo control recibió un volumen igual de agua destilada diariamente, durante 30 días por la misma vía. Las ratas fueron alimentadas con pienso obtenido a partir de alimentos de la casa Edo Feeds and Flour Mill Limited, Ewu, Edo state, Nigeria y bebieron agua libremente. Los animales se sacrificaron por el método de la dislocación cervical en el trigésimo primer día del experimento y el cerebro se extrajo cuidadosamente, siendo secado, pesado y grabado con la balanza Mettler Toledo.

Los resultados indican que hubo una disminución significativa ($P <0,05$) en el peso seco del cerebro y un aumento en el peso relativo del cerebro seco del grupo de tratamiento en comparación con el grupo control en este experimento (cuadro 1, figuras 1 y 2). También hubo un incremento significativo ($P <0,05$) en el peso seco del colículo inferior al peso total seco del cerebro en el grupo de tratamiento en comparación con el grupo control. Sin embargo, la relación peso seco colículo inferior fue significativamente mayor ($P <0,05$) en el grupo de tratamiento también diferente a la del grupo de control en este experimento(cuadro 1, figura 3).

PALABRAS CLAVE: Efavirenz. Ratas Wistar. Cerebro. Colliculus Inferior.

INTRODUCTION

Efavirenz is an antiretroviral drug that belongs to the class of drugs called non-nucleoside reverse transcriptase inhibitor (NNRTI) used as part of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type-1[1]. Efavirenz has been found to be effective in many combination regimes for the treatment of HIV infection, both in previously untreated and in treated individuals. It has been combined successfully with nucleoside consisting of lamivudine or emtricitabine plus abacavir, didanosine, stavidine, tenofovir or zidovudine to achieve virologic suppression in a high percentage of recipients[2,3]. Most antiviral agents do not efficiently penetrate the blood brain barrier (BBB) or are actively transported out of the central nervous system[4]. Even after antiviral treatment that successfully controls virus in the treatment compartments, the central nervous system may suffer continuing damage induced by HIV infection[5]. Efavirenz may be taken once a day without regards to meal and it can penetrate the central nervous system and spinal fluids[6,7].

Some adverse effect in the central nervous system has been commonly associated with efavirenz[8]. The most common central nervous system effects include confusion, insomnia, abnormal vivid dreams, dizziness and headache. Efavirenz has emerged as cornerstone of highly active antiretroviral therapy (HAART) regimens. The side effect profile of the drug is generally regarded as satisfactory. However, there are conflicting study results in the medical literature as well as conflicting studies from patients and physicians regarding the neuropsychiatric problems associated with efavirenz[9]. Lipodystrophy, moderate or severs pain, abnormal vision, arthralgia, asthenia, dyspnea, gynecomastia, myalgia, myopathy and tinnitus have been reported concerning efavirenz[1].

The inferior colliculus is the obligatory midbrain synaptic target of the ascending auditory pathway, in which the contralateral ear is represented primarily[10]. Inferior colliculus is essential for normal hearing and for the startle reflex. It receives its ascending input mainly from the contralateral cochlear nucleus and the superior olive and sends axons to the medial geniculate body[10].

Cortical structures such as the medial and lateral geniculate bodies, inferior and superior colliculi have higher glucose utilization than other structures[11]. There is a correlation between functional activity and metabolic rate such as in the visual and auditory system[11]. Since efavirenz crosses the blood brain barrier, it is relevant to investigate its effect on the brain and inferior colliculus. It is probable that the adverse effects of efavirenz on hearing such as tinnitus may be due to direct effect of efavirenz on the inferior colliculus. This present study was to elucidate the effects of chronic administration of efavirenz on the weight of the brain and inferior colliculus of the adult wistar rats.

MATERIALS AND METHODS

ANIMALS: Sixteen adult wistar rats of both sexes with average weight of 200g were randomly assigned into two groups; control (n=8) and treatment (n=8). The rats were obtained and maintained in the Animal Holding of the Department of Anatomy, School of Basic Medical Sciences, University of Benin, Benin City, Edo State Nigeria. They were fed with grower's mash obtained from Edo Feeds and Flour Mill Limited, Ewu, Edo State, Nigeria and given water liberally. Efavirenz was obtained from the PEPFAR unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

DRUG ADMINISTRATION: The rats in the treatment group received the recommended dosage of 600mg/70kg body weight of efavirenz dissolved in distilled water for thirty days through orogastric tube administration while the control rats received equal volume of distilled water through the same route and for the same period. The body weights of both groups were measured using Mettler Toledo weighing balance before and during the period of treatment.

DISSECTION OF THE BRAIN AND THE INFERIOR COLLICULUS: The rats in both groups were sacrificed by cervical dislocation and the skull was quickly opened with the aid of a pair of bone forceps to expose the brain. The brain was dried, weighed and recorded. The inferior colliculi were carefully dissected out, weighed and also recorded using the Mettler Toledo weighing balance.

STATISTICAL ANALYSIS: The mean values of the brain and inferior colliculus obtained from the control and treatment groups were recorded and compared statistically using the paired sample T-Test and Symmetric Measured Test of the Statistical Package for Social Sciences (SPSS)

RESULTS

BRAIN WEIGHT: There was a significant decrease ($P < 0.05$) in the brain weight of the treatment group as compared to that of the control group in this experiment. However, the relative brain weight of the treatment group was significantly higher ($P < 0.05$) than that of the control group when compared statistically (Table 1, figures 1 and 2).

	GROUP OF ANIMALS	
	CONTROL (n = 8)	TREATMENT (n = 8)
Brain wt (g)	1.85 ± 0.08	1.76 ± 0.20
Relative Brain Weight (%)	0.57 ± 0.04	0.66 ± 0.06
Inferior colliculus wt (g)	0.03 ± 0.02	0.06 ± 0.01
Relative Inferior colliculus wt (%)	1.71 ± 0.93	3.43 ± 0.46

Table 1: The Mean Weight (g) and Relative Weight (%) of the Brain and Inferior Colliculus (IC) of the Animals.

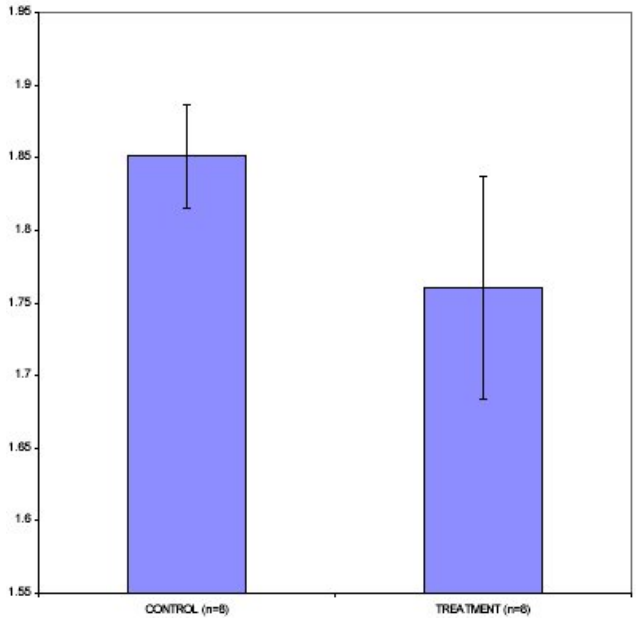

Figure 1: Bar Chart Showing the Brain Weight (g) of the Animals

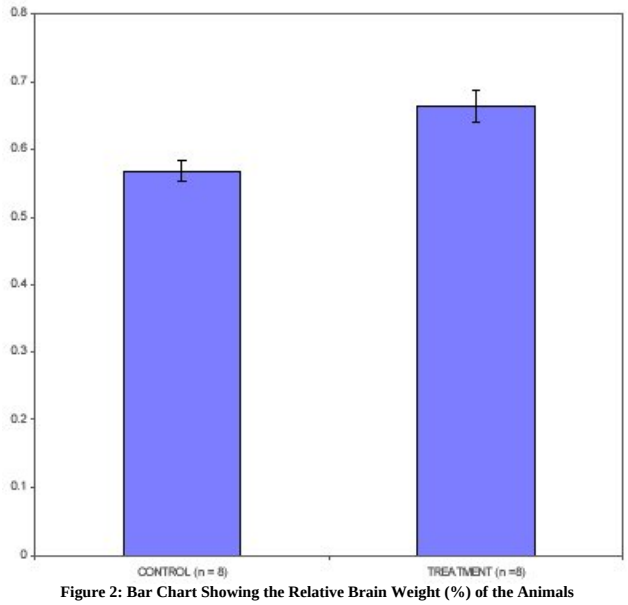

Figure 2: Bar Chart Showing the Relative Brain Weight (%) of the Animals

INFERIOR COLLICULUS WEIGHTS: There was a significant increase (P < 0.05) in the dry weight of the inferior colliculus per the total dry brain weight in the treatment group as compared to the control group. The relative inferior colliculus weight was also significantly higher (P < 0.05) in the treatment group than that of the control group in this experiment (Table 1, fig. 3 & 4)

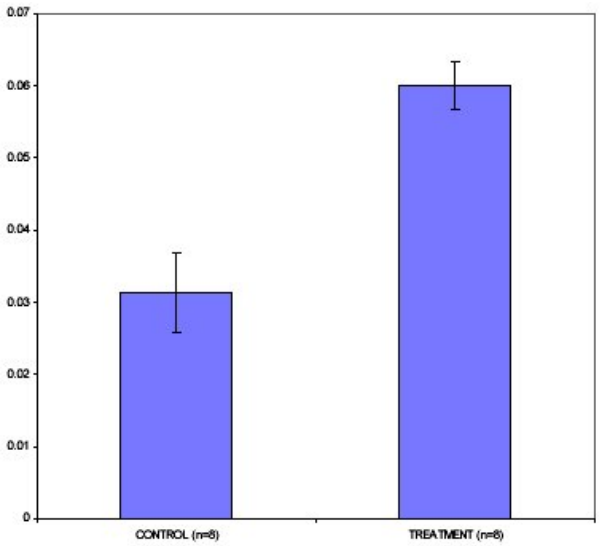

Figure 3: Bar Chart Showing the Inferior Colliculus Weight (g) of the Animals

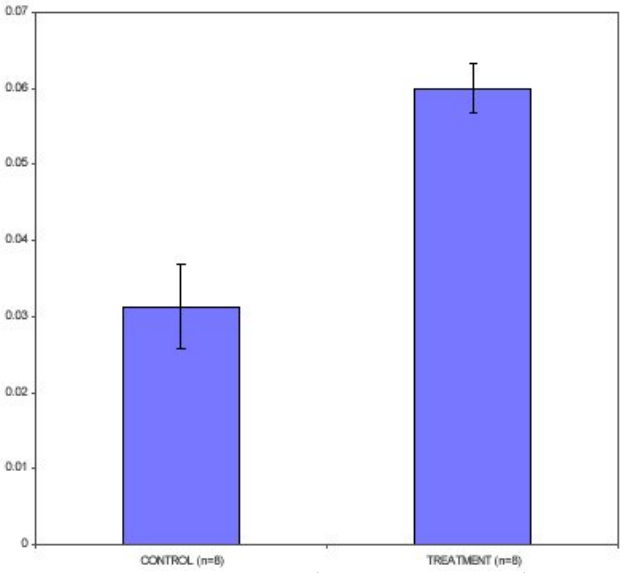

Figure 4: Bar Chart Showing the Relative Inferior Colliculus Weight (%) of the Animals

DISCUSSION

The result of this experiment revealed that chronic administration of efavirenz showed a significant decrease (P > 0.05) in the brain weight of the treatment group as compared to that of the control group in this experiment. However, the relative brain weight of the treatment group was significantly higher (P < 0.05) than that of the control group when compared statistically (Table 1, fig 1 & 2). The inferior collicullus weight of the treatment group was significantly higher (P 0.05) than that of the control group. The relative inferior colliculus weight of the treatment group was also significantly higher (P < 0.05) than that of the control group in this experiment (Table 1, fig. 3 & 4)

It has been reported that chronic administration of chloroquine affects the weight of the inferior collilculus in adult wistar rats[12]. Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the brain parenchyma. Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells[13]. Cytotoxic edema usually involves intracellular swelling of glial, endothelia and neurons 13. The weight of the inferior colliculus and the relative brain weight reported in this experiment to be significantly increased might due to neurotoxic effect of efavirenz on the cells of the brain and inferior collicus of the adult wistar rats.

There was a significant increase (P < 0.05) in the weight of the inferior colliculus and the relative brain weight in the treatment group as compared to the control group in this experiment. Regulation of brain water content and therefore of the volume is critical for maintaining the intracranial pressure within tolerable limits[13]. In this study efavirenz could have acted as toxins to the cell of the inferior colliculus and the relative brain weight thus affecting their cellular integrity and causing a defect in membrane permeability and cell volume homeostasis. Efavirenz is known to cross blood brain barrier and thus getting access to the cells of the brain. The prime candidates for inducing the massive cell increase observed in neurodegeneration are neurotoxins[14].

As brain tissue swells or shrinks as seen in this study, the activity of the cellular transporters is approximately modified by the up or down regulations as

earlier reported in the case of hyponatramia or hypernatremia[13]. Ischemia or pharmacologic disruption of cellular transporters can cause swelling of parenchyma of the brain and that of the inferior colliculus. The pharmacologic disruption of the brain and inferior colliculus weights caused by efavirenz is a cardinal feature of the results of this experiment. Though there are many different causes of cell swelling, including drug poisoning, water intoxication, hypoxia, and acute hyponatremia[13]. Under such conditions there is a net shift of water from the extracellular space to the interior of the brain cells[13]. The significant increase associated with the inferior colliculus and the relative brain weight in this experiment usually involves intracellular swellings of glial, endothelia and neurons[13]. Brains swelling attendant to severe cytotoxic edema may lead to marked reduction in the size of the ventricular system and basal cisterns[13].

The increase in weight observed in the treated relative brain weight and that of the inferior colliculus may be due to efavirenz interference. The toxic effects of efavirenz on the brain and inferior colliculus weights of the treated animals observed in this experiment may underline the possible neurological symptoms, such as tinnitus as reported following efavirenz treatment[1].

REFERENCES

1. American Hospital Formulary Service (AHFS): Drug Information. 2007; 686-694

2. Staszewski S, Miller V, Sabin C, Schlecht C, Gute P, Stamm S, Leder T, Berger A, Weidemann E, Hill A, Phillips A. Determinants of sustainable CD4 lymphocyte count increases in response to antiretroviral therapy. AIDS. 1999; 13: 951-956.

3. Gulick RM, Ribaudo HJ, Shikuma CM, Lalama C, Schackman BR, Meyer WA 3rd, Acosta EP, Schouten J, Squires KE, Pilcher CD, Murphy RL, Koletar SL, Carlson M, Reichman RC, Bastow B, Klingman KL, Kuritzkes DR; AIDS Clinical Trials Group (ACTG) A5095 Study Team. Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial. JAMA. 2006; 296, 769-781.

4. Schrager LK, D'Souza MP. Cellular and anatomical reservoirs of HIV-1 in patients receiving potent antiretroviral combination therapy. JAMA. 1998; 280:67-71.

5. Fox HS, Weed MR, Huitron-Resendiz S, Baig J, Horn TF, Dailey PJ, Bischofberger N, Henriksen SJ. ntiviral treatment normalizes neurophysiological but not movement abnormalities in simian immunodeficiency virus-infected monkeys. J Clin Invest. 2000;106:37-45.

6. The AIDS InfoNet: Efavirenz (Sustiva, Stocrin) Fact Sheet 432. Online: www.aidsinfonet.org/fact_sheets/view/432

7. Puzantian T. Central nervous system adverse effects with efavirenz: case report and review. Pharmacotherapy. 2002; 22: 930-933.

8. Ruiz NM, Bessen LJ, Manion DJ et al. Potential adverse experiences associated with efavirenz in adults. 6th Conference on Retroviruses and Opportunistic Infections. Chicago, IL, February 1999, Abstract 655.

9. Baker R. Central Nervous System Toxicities and Efavirenz. 2006

10. Fall. Mammalian Neuroanatomy MCB 163, 1999

11. Siesjo B K. Utilization of Substrates by Brain Tissues. Brain energy metabolism. Ed. John Wiley & Sons. USA. 1978; 101-130.

12. Adjene JO, Adenowo TK. Effects of Chronic Administration of Chloroquine on the Weight of the Intracranial Auditory Relay Centers of Adult Wistar Rats. J Med Biomed Res 2005; 4: 70-74.

13. Johanson CE. Effects of Fluid in Balances. Neurosciene in Medicine. P. Michael Conn, J.B. Lippincott Company, 1995; 187-189.

14. Waters CM, Moser W, Walkinshaw G, Mitchell IJ. Death of neurons in the neonatal rodent and primate globus pallidus occurs by a mechanism of apoptosis. Neuroscience 1994; 63: 881 - 894.

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Comment of the reviewer José María Trejo Gabriel y Galán. MD, PhD. Jefe de S. de Neurología del Hospital General Yagüe. Burgos. España.

The AIDS antiretroviral agent efavirenz has neuropsychiatric secondary effects difficult to discern from the disease itself so basic science investigations of their central nervous system effects are welcome.

Comment of the reviewer Prof. D. José María Eirós Bouza. MD, PhD. Titular de Microbiología de la Facultad de Medicina de la Universidad de Valladolid. Valladolid. España

Basic contributions that can elucidate the secondary effects of antiretrovirals are always welcome, due to the wide variability in the use of these drugs. In the present work by Adjene and Arukwe they make a contribution on the delimiting effect of a non-nucleoside reverse transcriptase inhibitor (Efavirenz) on rat brains, protected from the potential neuropsychiatric effect seen in patients with HIV infection treated with this drug.

In the article they list a series of macroscopic and microscopic changes in the variables in the of the treated rat group compared to the control group. It makes clear that this is a preliminary step to its extrapolation in human beings. However, the fact that it was performed in the University of Benin

Department of Anatomy must support its publication and deserves to be mentioned.

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