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Effects of Chronic Administration of Efavirenz on the Body and Brain Weights of Adult Wistar Rats

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ABSTRACT

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 body and brain weights of adult wistar rats were carefully studied. The rats of both sexes (n=16), with the average weight of 200g were randomly assigned into treatment (n=8) and control (n=8) groups. The rats in the treatment group received 8.57mg/kg bogy 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. The brains were carefully dissected out, dried and weighed using the Mettler Toledo weighing balance. The body weights were taken before and during the period of treatment using the weighing balance.The findings indicate that there was a steady increase in the body weight during the period of acclimatization and before the treatment. During treatment, the control animals continues to increase in body weight, while that of the treatment group showed decrease in body weight that was statistically significant ($P < 0.05$) when compared with the control group.There was also a significant decrease ($P < 0.05$) in the dry brain weight and a significant increase ($P < 0.05$) in the relative dry brain weight of the treated group as compared to the control group in this experiment.

Keywords: Effects, Efavirenz, Body weight, Brain weight, Wistar Rats.

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 (AHFS 2007). Efavirenz has been found to be effective in many combination regimes for the treatment of HIV infection, both in previously untreated and in treatment experienced individuals. It has been combined successfully with nucleoside backbone consisting of lamivudine or emtricitabine plus abacavir, didanosine, stavidine, tenofovir or zidovudine to achieve virologic suppression in a high percentage of recipients (Staszewski et al 1999, Gulick et al 2006). Most antiviral agents do not efficiently penetrate the blood brain barrier (BBB) or are actively transported out of the central nervous system (Schranger & D'Souza 1998). Even after antiviral treatment that successfully controls virus in the treatment compartments, the central nervous system may suffer continuing damage induced by HIV infection (Fox 2000). Efavirenz may be taken once a day without regards to meal and it can penetrate the central nervous system and spinal fluids (AIDS INFONET 2007, Puzantian 2002).

Some adverse effect in the central nervous system has been commonly associated with efavirenz (Ruiz et al 1999). 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 (Baker 2006). Lipodystrophy, moderate or severs pain, abnormal vision, arthralgia. Asthenis, dyspnea, omastia myalgia, myopathy and tinnitus have been

reported concerning efavirenz(AHFS 2007).

Caloric restriction and body weight have independent effects on mortality rate in wistar rat (Wang et al 2004). Body weight appeared to be a better indication of maturity than time (Pullen 1976). Weight gain is usually the result of an imbalance between calorie in take and the body's energy expenditure. Heavy alcoholic intake contributed directly to weight gain and obesity regardless of the type of alcohol consumed (Wannamethee & Shaper 2003). The brain and nervous system regulate body weight and control appetite and food intake. Dietary quinine reduces body weight and food intake independent of aversive taste (Heybach and Boyle 1982). Ingestion of diets containing equal amount of quinine resulted in equivalent chronic body weight reduction, despite different diet characteristics (Heybach and Boyle 1982). Presence of reduction in the food consumption and body weight gains of rats that fed on a diet containing quinine dehydrochloride for four weeks has been reported (Colley, et al 1982). Neonatal exposure to ethanol vapour resulted in decreased body and brain weight as well as microcephaly (Bellings et al 2002). This present study is to elucidate the effects of chronic administration of efavirenz on the body and brain weights of 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 PEPFER unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

Drug Administration: The rats in the treatment group received 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: 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 using the Mettler Toledo weighing balance.

Statistical Analysis: The values obtained from the body and brain weights of the control and treatment groups were recorded and compared using the statistical package for social sciences (SPSS).

RESULTS

Body Weight: There was a steady increase of the body weight in both the treatment and control groups during the period of acclimatization and before the treatment. During treatment the rats in the control group continues to increase in body weight, while that of the treatment group showed decrease in weight that was significant ($P<0.05$) when compared statistically with the control group(Table1,Fig1).

Brain Weight: There was a significant decrease ($P < 0.05$) between the brain weight of the control and treatment groups 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 compare statistically (Table 2, fig 2 and 3).

DISCUSSION

The result of this research revealed that chronic administration of efavirenz showed a significant decrease ($P<0.05$) in the body weight of the treatment group as compared to that of the

Table 1: The Mean Body Weight (g) Of The Animals

No of days (week)	Group of Animals	
	CONTROL (n = 8)	TREATMENT (n = 8)
-2	245 ± 32.53	240 ± 28.28
-1	250 ± 8.16	275 ± 0.00
0	264 ± 13.53	276 ± 4.27
1	275.8 ± 11.61	271 ± 13.48
2	286 ± 8.63	272 ± 15.55
3	305.8 ± 11.77	272.6 ± 17.87
4	327.6 ± 15.76	265.5 ± 14.09
P-value (P<0.05):	Significant	

Table 2: The Mean Weight (g) of the Body and Brain of the Animals

	Group of Animals	
	CONTROL (n = 8)	TREATMENT (n = 8)
Body weight (g)	327.64 ± 15.76	265.8 ± 14.09
Brain Weight(g)	1.85 ± 0.09	1.76 ± 0.201
Relative Brain Weght (%)	0.57 ± 0.04	0.66 ± 0.06
P-value (P<0.05):	Significant	

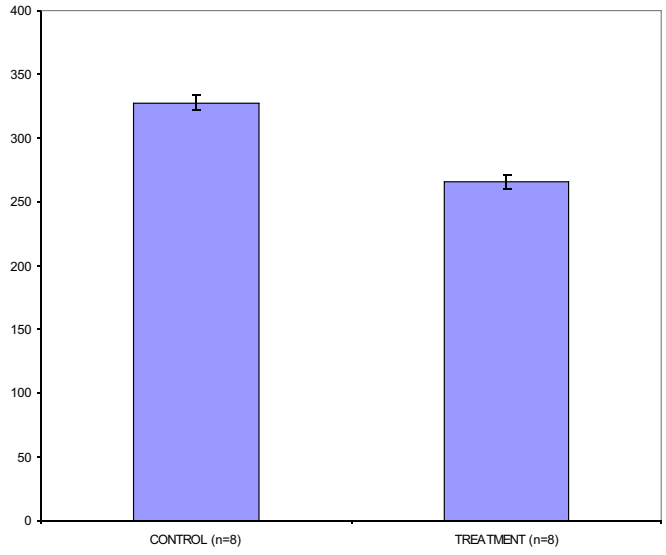

Fig 1: Bar Chart Showing the Body Weight (g) of the Animals.

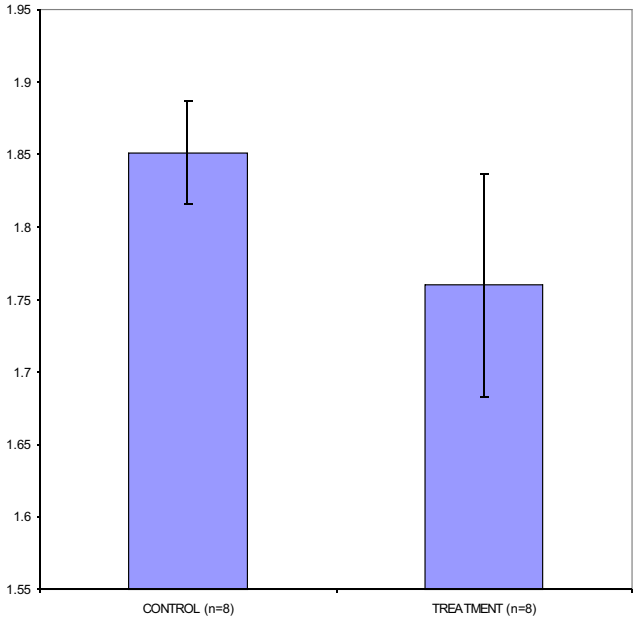

Fig 2: Bar Chart Showing the Brain Weight (g) of the Animals

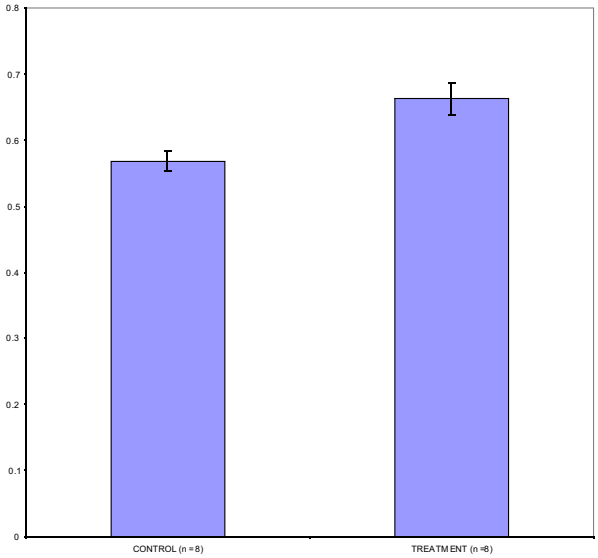

Fig 3: Bar Chart Showing the Relative Brain Weight (%) of the Animals

Control group. There was a significant decrease (P>0.05) in the brain weight of the treatment group as compared to the control group, whereas the relative brain weight of the treatment group was significantly higher (P<0.05) than that of the control group.

The drug might probably promote satiety hence reduces weight gain. (Johanson 1995). It has been reported that chronic administration of chloroquine affects the weight of inferior collilculus in adult wistar rats (Adjene and Adenowo 2005). Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the brain parenchyma (Johanson 1995). Under such conditions, there is a net shift of water from the

extracellular space to the interior of the brain cells (Johanson 1995). Cytotoxic edema usually involves intracellular swelling of glial, endothelia and neurons (Johanson 1995). The weight of the brain reported in this experiment to decrease significantly might be due to the neurotoxic effect of efavirenz on the cells of the brain in the adult wistar rats.

There was a significant decrease ($P<0.05$) in the weight of the brain and an increase in the relative brain weight in the treatment group as compared to the control group. Regulation of brain water content and therefore of the volume is critical for maintaining the intracranial pressure within tolerable limits (Johanson 1995). In this study efavirenz could have acted as toxins to the cell of the brain and thus affecting their cellular integrity. This causes a defect in membrane permeability and cell volume homeostasis in the brain. Efavirenz is known to cross blood brain barrier and thus getting access to the cells. The prime candidates for inducing the massive cell increase or decrease observed in any neurodegeneration are neurotoxins (Waters et al 1994).

As brain tissues 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 (Johanson 1995). Ischemia or pharmacologic disruption of cellular transporters can cause swelling of parenchyma of the brain. The pharmacologic disruption of 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 (Johanson 1995). Under such conditions there is a net shift of water from the extracellular space to the interior of the brain cells (Johanson 1995). The significant decrease associated with the body, and brain weights in this experiment usually involves the intracellular glial cells, endothelia and neurons (Johanson 1995). Brain swelling attendant to severe cytotoxic edema may lead to marked reduction in the size of the ventricular system and basal cisterns as reported by Johanson, 1995.

The decrease in weight observed in the stroma of the treated body and brain weight and an increase in the relative brain weight may be due to efavirenz interference.The brain and nervous system regulate body weight and control appetite and food intake. Dietary quinine reduces body weight and food intake independent of aversive taste which is in line with this experiment concerning efavirenz (Heybach and Boyle 1982). Ingestion of diets containing equal amount of quinine resulted in equivalent chronic body weight reduction, despite different diet characteristics (Heybach and Boyle 1982). The toxic effects of efavirenz on the weight of the treated animals observed in this experiment may underline the possible neurological symptoms, such as tinnitus as reported following efavirenz treatment (AHFS, 2007).

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