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Effects of Chronic Administration of Zidovudine (AZT) on the Body and Brain Weights of Adult Wistar Rats

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ABSTRACT

The effects of chronic administration of Zidovudine (AZT) commonly used as part of highly active antiretroviral therapy (HAART) for the treatment of Human Immunodeficiency Virus (HIV) type-1 therapy on **the** body and brain weights of adult wistar rats were carefully studied. The rats of both sexes (N=40), with an average weight of 200g were randomly assigned into tested (n_1=20) and control (n_2=20) groups. The rats in the tested group received 300mg/70kg (0.857mg/200g) body weight of AZT being the dosage required twice daily dissolved in distilled water and given 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 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 weresacrificed by cervical dislocation method on the thirty-first day of the experiment. The brainswere carefully dissected out, blotted dried and quickly weighed using Toledo weighing balance.The values obtained from the experiment were recorded and compared statistically using the unpaired sample T-test and symmetric measured test of the Statistical Package for Social Sciences (SPSS).The findings of this experiment revealed that there was a steady increase in the body weight**(g)** of both groups during the period of acclimatization and before the drug administration. During treatment the rats in the control group continues in a steady increase in body weight, while that of the tested group showed increase in body weight that was statistically significant ($P<0.05$) when compared with the control group.There was a significant increase ($P < 0.05$) in the brain weight (g) of the tested group as compared to the control. However, the relative brain weight (%) of the tested group was significantly ($P < 0.05$) lower as compared to the control group.Chronic administration of zidovudine may have an adverse effect on the body and brainweights of adult wistar rats. It is recommended that further studies aimed at corroborating these observations be carried out.

Keywords: Zidovudine, Weight effects, Body, Brain, Wistar Rats

INTRODUCTION

Zidovudine (AZT) is a type of medicine called a nucleoside reverse transcriptase inhibitor (NRTI). It works by disrupting one of the early steps in the HIV life cycle, called reverse transcription. It is used as part of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type-1 [1]. AZThas been found to be effective in many combination regimens for the treatment of HIV infection. It has been combined successfully with efavirenz and other nucleoside consisting of lamivudine or emtricitabine plus abacavir, didanosine, stavidine, or tenofovir 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].

Combination antiretroviral regimens have revolutionized the treatment of HIV infection, which has resulted in dramatic reductions in morbidity, mortality, and health care utilization [6]. Effective antiretroviral therapy (ART) consistently results in sustained suppression of HIV-1 RNA replication resulting in gradual increases in CD4 T-lymphocyte count, sometimes to normal levels [7]. ART does not eradicate the virus as viral replication continues in lymphoid tissue despite suppressive treatment [8,9]. However, durable suppression of viral replication and the accompanying increases in CD4 count, reverse HIV disease progression, even in persons with advanced HIV infection [10]. It is now possible to achieve at least

transient reversal of disease progression in almost all patients who have received no prior ART, as HIV strains present in these "treatment-naïve" antiretroviral drug [11].

AZT may be taken twice a day and it can penetrate the central nervous system and spinal fluids [12]. Some adverse effect in the central nervous system has been commonly associated with AZT. The most common central nervous system effects include confusion, insomnia, abnormal vivid dreams, dizziness, headache, tinnitus and abnormal vision. However, *in vitro* studies confirmed that AZT, zalcitabine and didanosine are substrates for several nucleoside transporters [13,14]. It has been reported that, although AZT penetrates CSF through the blood- CSF barrier at the choroids plexus, its transport into the brain is restricted [15].

AZT treatment also reduced HIV-1 induced brain lesions in neuropathological studies of patients with AIDS [16]. Termination of AZT treatment rapidly increased the incidence of HIV-1 encephalitis again[17,18].

Continued therapy of AZT with didanosine (ddI) after interrupted AZT treatment has been reported to protect patients against HIV-1 encephalitis [19]. But the incidence of HIV-1 related dementia is high during ddImonotherapy[20]. In addition to its prophylactic effect, AZT also offers benefits in the treatment of established HIV-1 related dementia [21,22].

It would therefore be worthwhile to examine the effects of chronic administration of AZT on the body and brain weights of adult wistar rats.

MATERIALS AND METHODS

Animals care and Ethics: The Faculty of Basic Medical Sciences, Delta State University, Abraka granted approval before the commencement of the work. Forty adult wistar rats of both sexes with an average weight of about 200g were randomly assigned into two groups: control (n_1=20) and treatment (n_2=20). The rats were obtained and maintained in the Animal Holding of the Department of Anatomy and cell Biology, Faculty of Basic Medical Sciences, Delta State University, Abraka. They were fed with grower's mash obtained from Edo Feeds and Flour Mill Limited, Ewu, Edo State, Nigeria and given water liberally. Zidovudine was obtained from the President Emergency Plan for AIDS Relief (PEPFAR) Unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

Drug Administration: The rats in the treatment group received 300mg/70kg (0.857mg/200g) body weight of zidovudine being the dosages required twice daily. The drug was dissolved in distilled water and administered twice daily for thirty days through the orogastric tube while the control rats received equal volume of distilled water through the same route and for the same period.

The rats were sacrificed through cervical dislocation on the thirty-first day of the experiment and the brain of each animal was extracted, weighed and recorded using Mettler Toledo weighing balance. The values obtained from the control and treatment groups were recorded and compared statistically using the unpaired sample T-test and symmetric measured test of the Statistical Package for Social Sciences (SPSS)

RESULTS

The findings of the experiment revealed that there was a steady increase in the body weight of both groups during the period of acclimatization and before the drug administration. During treatment the rats in the control group continues in a steady increase in body weight, while that of the tested group showed increase in body weight that was statistically significant ($P<0.05$) when compared with the control group (Table1 fig.1& 2).

There was a significant increase ($P < 0.05$) in the brain weight of the tested group as compared to the control in this experiment. However, the relative brain weight of the tested group was significantly ($P < 0.05$) lower as compared to the control group (Table 2 fig.3 & 4).

Table 1: The mean SEM body weight (g) of the animals

No. of days (weekly)	Group of Animals	
	Control (n=20)	Tested(n=20)
- 2	178.5± 5.2	*180.6 ± 4.3
- 1	187.1 ± 9.3	*190.0 ± 3.9
0	*195.7 ± 7.0	*200.7 ± 5.5
1	*196.4 ± 7.7	*207.9 ± 5.5
2	*204.3 ± 10.2	*217.9 ± 5.6
3	*198.6 ± 8.1	*204.3 ± 5.3
4	*191.4 ± 7.6	*214.3 ± 5.7

*Significant ($P< 0.05$)

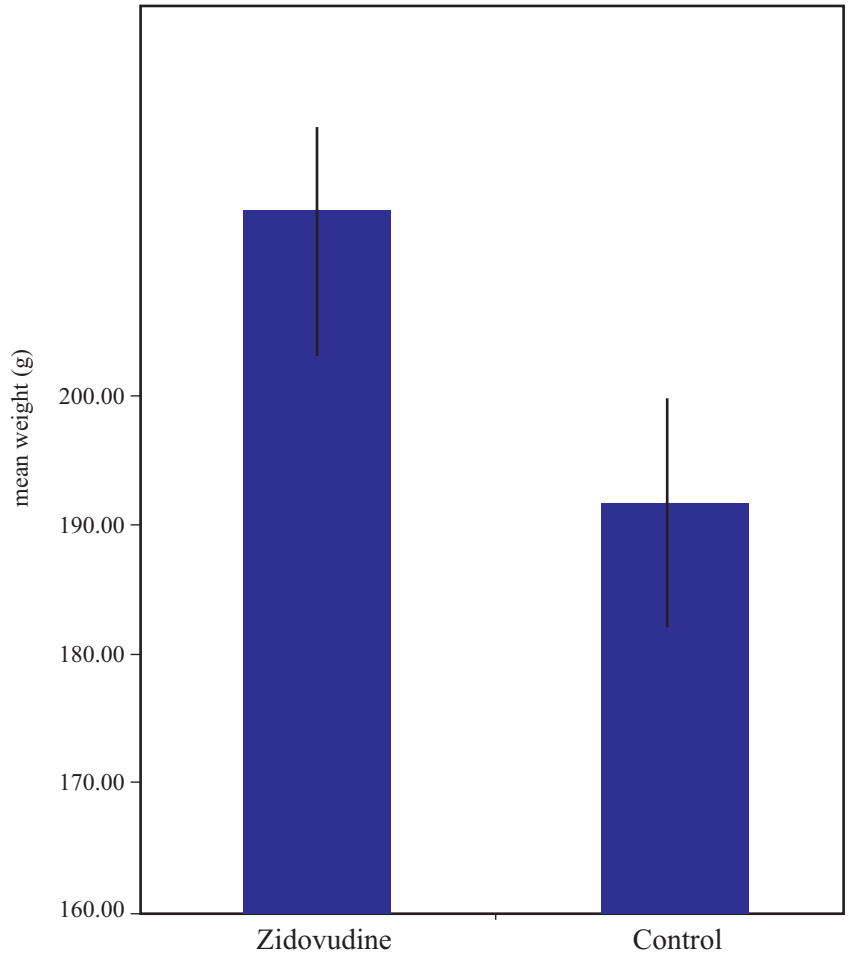

Figure 1: Bar chart showing the mean SEM body weight (g) of the animals

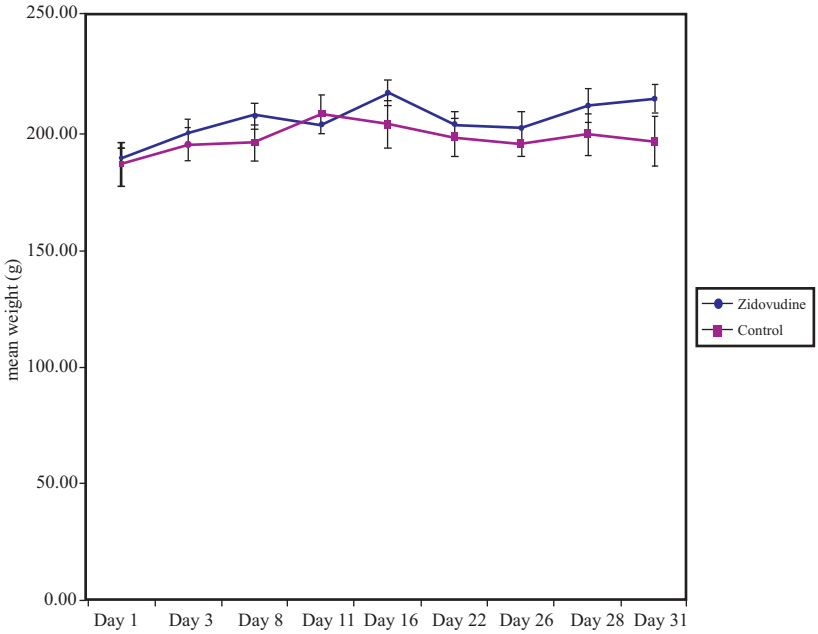

Figure 2: Line chart showing the mean body weight (g) of the animals

Table 2: The mean body and mean brain weight (g) of the animals

	Group of Animals	
	Control (n=20)	**Tested (n=20)**
Body weight (g)	**191.4 ± 7.6**	***214.3 ± 5.7**
Brain weight (g)	***1.65 ± 0.03**	***1.81 ± 0.04**
Relative Brain weight (%)	***0.87 ± 0.02**	***0.85 ± 0.03**

*Significant (P< 0.05)

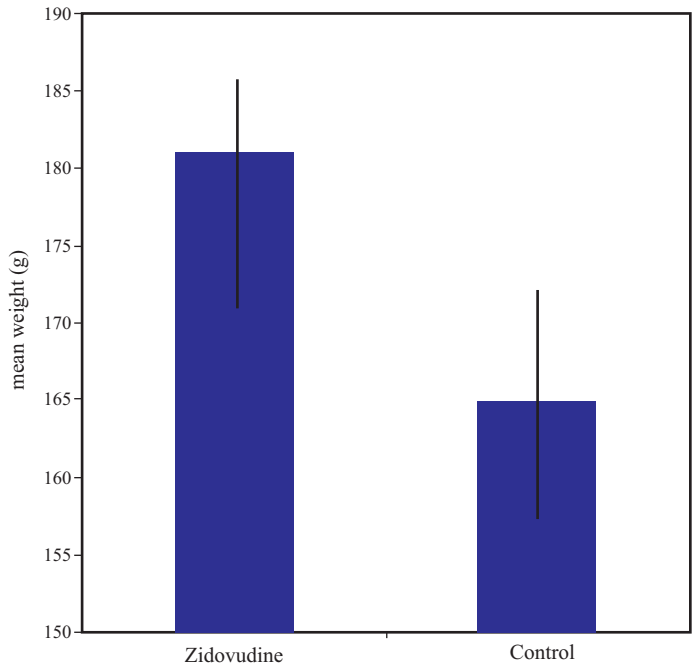

Figure 3: Bar chart showing the mean brain weight (g) of the animals

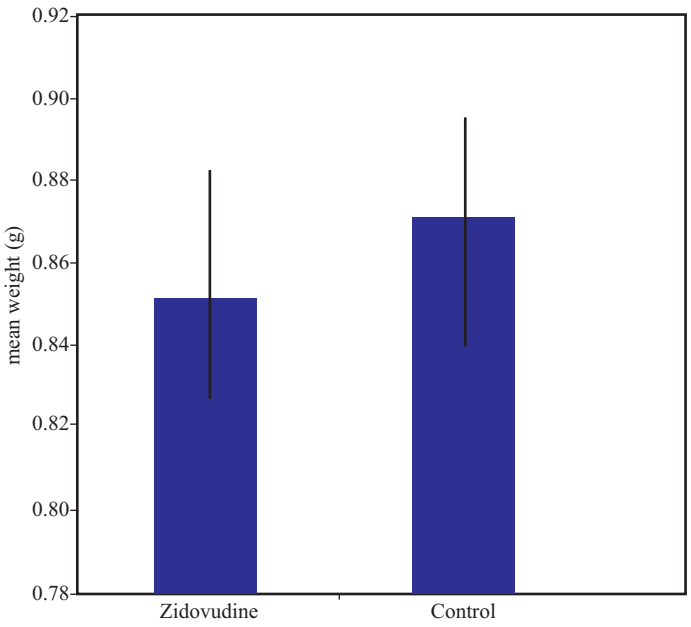

Figure 4: Bar chart showing the mean relative brain weight (%) of the animals

DISCUSSION

The result of this experiment revealed that chronic administration of zidovudine showed a significant (P<0.05) increase in the body and brain weights of the tested group as compared to the control group.The relative brain weight (%) of the tested group was significantly (P<0.05) reduced as compared to the control group.

It has been reported that chronic administration of chloroquine affects the weight of inferior collilculus in adult wistar rats [23]. Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the brain parenchyma [24]. Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells[24]. Cytotoxic edema usually involves intracellular swelling of glial, endothelia and neurons [24]. The weights of the body and brain reported in this experiment to be significantly(P<0.05) increased might be due to the neurotoxic effects of zidovudine on the cells of the body and brain of the adult wistar rats.

The significant(P<0.05) increased in the weight of the body and brain in the tested group as compared to the control group in this experiment might be due to the toxic effects of zidovudine.Regulation of brain water content and therefore of the volume is critical for maintaining the intracranial pressure within tolorable limits [24]. In this study,zidovudine could have acted as toxins to the cell of the body and brain, thus affecting their cellular integrity and causing a defect in membrane permeability and cell volume homeostasis. Zidovudinehas been 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 or decrease observed in neurodegeneration are neurotoxins [25].

As brain tissue swells and as seen in this study, the activity of the cellular transporters is approximately modified by the up or down regulations as it has been reported in the case of hyponatramia or hypernatremia [24]. Ischemia or pharmacologic disruption of cellular transporters can cause swelling of parenchyma of the brain. The pharmacologic disruption caused byzidovudinewas 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[24].

Under such conditions, there is a net shift of water from the extracellular space to the interior of the brain cells [24]. The significant(P<0.05) increase associated with the body and brainweights with an associated significant(P<0.05) decrease in the relative brain weight in the tested group as compared to the control group in this experiment may involves intracellular swellings or shrinkage of the glial, endothelia and neurons cells of the tested group [24]. Brains swelling attendant to severe cytotoxic oedema which may lead to marked reduction in the size of the ventricular system and basal cisterns [24].

The significant (P<0.05) increase in the body and brain weights observed in this experiment may be due to zidovudine 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 that is in line with this experiment concerning zidovudine[26].

Ingestion of diets containing equal amount of quinine resulted in equivalent chronic body weight reduction, despite different diet characteristics [26].Caloric restriction and body weight have independent effects on mortality rate in wistar rat[27]. Body weight appeared to be a better indication of maturity than time [28]. Weight gain is usually the result of an imbalance between calorie intake and the body's energy expenditure.

Heavy alcoholic intake contributed directly to weight gain and obesity regardless the type of alcohol consumed [29]. 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 [30]. Neonatal exposure to ethanol vapour resulted in decreased body and brain weight as well as microcephaly [31].

The toxic effects of zidovudine on the body and brain weights of the testedanimals observed in this experiment may underline the probable neurological symptoms associated with zidovudine treatment in humans.

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