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RESEARCH PAPER

EFFECT OF ZIDOVUDINE ON THE LIVER FUNCTION OF ADULT ALBINO WISTAR RATS

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ABSTRACT

Zidovudine is a type of antiretroviral drug used for the treatment of human immunodeficiency virus (HIV) infection. This study investigated its effect on liver enzymes in adult male albino rats. Fifteen male albino rats weighing between 180-250g were used for the study. The rats were subdivided into a control (A) and two test groups (B and C) (n=5 each). For 25 days, the test groups (B and C) received a daily dosage of 6mg/kg and 12mg/kg of the drug solutions (in sterile water) via an oral cannula, while the control group (A) received normal feed and water only. The results showed that Zidovudine caused significant increase in the level of alanine transaminase (ALT) in the high-dose treated rats, but no significant change in aspartate transaminase (AST) and alkaline phosphatase (ALP) in both the high and low-dose treated rats; and alanine transaminase (ALT) in the low-dose treated rats. Our findings suggest that high dose of Zidovudine can induce increase in the level of ALT in the treated animals. It also demonstrates that the use of antiretroviral drugs could have adverse effects on the liver that could lead to hepatic damage in normal subjects as the experimental rats used were HIV free.

Key Words: Liver, Enzymes, HIV/AIDS, Zidovudine

INTRODUCTION

With the increasing prevalence of HIV/AIDS, different antiretroviral drugs have been used to combat the progression of the disease. One of such drugs is Zidovudine which is a potent inhibitor of replication of HIV cells (Wright, 2004). It is phosphorylated in both infected and non-infected cells to monophosphate (MP) -a derivative of cellular thymidine kinase, and subsequently phosphorylated to diphosphate and then to a triphosphate (TP). This process is catalyzed by the enzyme cellular thymidine kinase and AZT-TP acts as an inhibitor substrate for the viral reverse transcriptase. Usually, the formation of further pro-viral DNA is blocked by the incorporation of MP into the chain and subsequently a chain termination competition by AZT-TP occurs. According to Wright (2008), HIV reverse transcriptase is approximately 100 fold greater compared to cellular DNA polymerase alpha.

On the other hand, the liver is one of the major organs involved in the metabolism of food and foreign substances including drugs. It performs more than 500 vital metabolic functions (Wilson, 2008). It is involved in the synthesis of products like glucose, plasma proteins, clotting factors and urea released into the blood stream. Hence the effect of zidovudine on liver functions is of paramount importance and should not be overlooked. Therefore, this study is intended to determine the effect of Zidovudine on liver function with the specific objectives of assessing the effect of zidovudine on body weight, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT).

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MATERIALS AND METHOD

Drug of Study: The antiretroviral drug considered in this study is a single-dose zidovudine tablet (300mg). It was obtained from the antiretroviral unit of the Central Hospital, Agbor, Delta State, Nigeria, but manufactured by Aurobindo Pharma Limited, Unit 3, Survey No. 313, Bachupally Village, Quthubullapur Mandal, Ranga Reddy District (A.P), India.

Animal care and handling: Fifteen (15) male albino Wistar rats weighing 180-250 grams were purchased from the animal house of Ambrose Alli University (AAU), Ekpoma, Edo State, Nigeria, and maintained under a controlled condition of temperature (33±2%), humidity and light (12 hours of light and dark) in the animal house of Delta State University, Abraka, Delta State, Nigeria. The animals were fed twice daily with standard pellet diet -grower mash and clean tap water. The animals were housed in a standard environmental condition in wire-mesh-bottomed wooden cage and allowed to acclimatize for seven (7) days before drug administration.

Experimental design: Fifteen (15) male Albino wistar rats weighing between 180-250grams were randomly assigned into three (3) groups (A, B and C) (n=5 each). Groups B and C served as test groups while A served as control. Relying on the therapeutic dose of zidovudine in humans (300mg), the corresponding therapeutic dose for rat models was calculated and aqueous formulated solution was administered as follows: rats in group B and C received 6mg/kg (low dose) and 12mg/kg (high dose) per day respectively for 25 days, while the rats in group A received normal feed and water only. All administrations were performed via oral intubations.

Blood sample collection and analysis: Having anaesthesized the rats in a chloroform saturated chamber, blood samples were collected by cardiac puncture using 5m1 hypodermal syringe and needle, and placed in an anticoagulant bottle. The serum was used for the assay of the hepatic enzymes activities (AST, ALT and ALP), using the Humazym Muv-test kits.

Estimation of the transaminase: Aspartate transaminase (AST) and Alanine transaminase (ALT) activities were assayed by the Reitman and Frankel method (Ashwood and Border, 1996) using Beckman spectro photometer.

Alkaline phosphate estimation: The method of King and Armstrong (Reiching and Kaplan, 1988) was employed for the estimation of alkaline phosphatase (ALP).

Statistics analysis: Data was analyzed separately using paired t-test and results were expressed as mean ± standard deviation to determine significant differences between means. $P< 0.05$ was regarded a significant.

RESULTS

After careful application of all the procedures outlined above, the results obtained showed that Zidovudine caused significant increase in the level of alanine transaminase (ALT) in the high-dose treated rats, but no significant change in aspartate transaminase (AST) and alkaline phosphatase (ALP) in both the high and low-dose treated rats, and alanine transaminase (ALT) in the low-dose treated rats (*see* tables 1, 2, 3, 4 and 5).

Table 1: Showing the effect of Zidovudine on the body weight of wistar rats

BODY WEIGHT (g)			
GROUPS	**INITIAL**	**FINAL**	**WEIGHT DIFFERENCE**
CONTROL	206.6 ± 92.39	210.0 ± 93.91	3.4 ± 1.52
LOW DOSE	186.0 ± 83.18	187.2 ± 83.72	1.2 ± 0.08
HIGH DOSE	190.0 ± 84.97	190.0 ± 84.97	0.0 ± 0.1

Values were express in mean ± standard error of mean (S.E.M) (n=5). There was no significant increase in body weight (P>0.05).

Table 2: Showing the comparison of body weight of control and low dose treated rats.

GROUP	CONTROL	LOW DOSE	T- CAL	T- TAB	P- VALUE	REMARK
BODY WEIGHT DIFFERENCE (g)	3.4 ± 1.52	1.2 ± 0.08	3.23	2.31	P<O.05	Significant

Result presented in mean ± SD (n=5). There was a significant increase in the body weight of the zidovudine low dose treated wistar rats when compared with the control (P>0.05).

Table 3: Showing the comparison of body weight of control to high dose treated rats

GROUP	CONTROL	HIGH DOSE	T-CAL	T-TAB	P-VALUE	REMARK
BODY WEIGHT DIFFERENCE (g)	3.4 ± 1.52	0.0± 0.1	5.0	2.31	P<0.05	Significant

Result presented in mean ± SD (n = 5).There was a significant increase in the body weight of the wistar rat treated with zidovudine in high dose (12mg/kg) for 25 days when compared to the control.

Table 4: Showing the effect of zidovudine on the liver function in low dose (6mg/kg) treated rats

GROUP	CONTROL	LOW DOSE	T-CAL	T- TA	P- VALUE	REMARK
AST (U/L)	18.2±9.55	14.6±4.34	0.77	2.31	P>0.0 5	Not Significant
ALT (U/L)	11.8±1.095	12.6±3.70	0.58	2.31	P>0.05	Not Significant
ALP (U/L)	286.74±147.82	197.37±24.798	1.3	2.31	P>0.0 5	Not Significant

Result presented in mean ± SD (n = 5).There was no significant change in the level of AST, ALT and ALP of the wistar treated for 25 days with zidovudine in low dose when compared with the control. **Key**: AST: Aspartate Transaminase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphate

Table 5: Showing the effect of zidovudine on the liver function in high dose (12mg/kg) treated rats

GROUP	CONTROL	LOW DOSE	T-CAL	T- TA	P- VALUE	REMARK
AST (U/L)	18.2±9.55	23.8±9.86	0.6	2.31	P>0.0 5	Not Significant
ALT (U/L)	11.8±1.095	15.8±2.28	3.5	2.31	P>0.05	Significant
ALP (U/L)	286.74±147.82	353.44±245.78	0.52	2.31	P>0.0 5	Not Significant

Result presented in mean ± SD (n = 5).There was no significant change in the level of AST and ALP of the wistar rat treated for 25 days with zidovudine in high dose when compared with the control but there was a significant increase in ALT (P<O.05) when compared with the control. **Key**: AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; ALP: Alkaline Phosphate

DISCUSSION

Hepatic toxicity appears to be a more frequent consequence of long term (3-12 months) exposure to zidovudine and increases in liver enzyme activity have been accompanied by hepatomegaly with macro vesicular steatosis and frequently, fatal lactic acidosis (Freiman *et al*., 1993; Chariot *et al*., 1991). In this study, the effects of zidovudine

(an antiretroviral drug) on some liver enzymes were examined. We demonstrated a statistically significant increase in the level of ALT after treatment with zidovudine in high dose for 25 days.

However, there was no significant change on the weight, AST and ALP, after the course of treatment in both high and low dose of zidovudine. There are several possible explanations for the observed increase in the level of ALT; though the exact mechanism by which zidovudine cause adverse hepatic effect has not been elucidated. William (1995) had reported that zidovudine induces liver injury occurs via at least six mechanisms involving various intracellular organelles, with consequent disruption of intracellular calcium homeostasis, decline in ATP levels and finally, hepatocyte swelling and rupture (Beanuc, 1987; Yun *et al*., 1993).

As indicated by the results of this study, only ALT was observed to have increased significantly at high dose of zidovudine administration for 25 days and available scientific evidence show that an elevation of this enzyme suggests hepatic damage, which often results from several mechanisms including the generation of free oxygen radicals and peroxidation of membranes e.t.c. (Urnar *et al*., 2008). It could be concluded therefore, that HIV patients on regular use of HAART containing zidovudine, may be at risk of liver damage.

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AUTHOR(S) CONTRIBUTIONS

This research work provide an empirical bases on the harmful effect of long term use or overdose of zidovudine and this will enable clinicians to make better judgment on its use especially in HIV patients with hepatic disease. The concept was designed by Dr Naiho A .O and laboratory bench work was carried out by Aloamaka C .O and Nwoche C .N.