Hepatotoxicity Effect Of Zidovudine On The Liver

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Abstract: The introduction of potent combination antiretroviral therapy (ART) in the treatment of HIV infection has permitted the reliable control of disease progression and has markedly improved survival among people with HIV. As a result health care providers and patients has shifted clinical priorities as well as once delaying opportunistic illness was a primary focus increasing emphasis is now placed on preventative health, management of comorbid chronic disease and avoiding long term toxicities of ART. A total 63 Wister Albino rats of weight range (124 – 197g) were divided into five (5) groups (n = 5) labeled A, B, C, D, and E. Group A served as the control group while groups B, C, D, and E were the treatment groups which was done orally with 4 different doses (0.7mg/KgBw, 1.4mg/KgBw, 2.1mg/KgBw and 2.8mg/KgBw respectively for 4 weeks. Animals were sacrificed weekly and the liver was collected for histological examination for 4 weeks. The research found out that the different concentrations of Zidovudine has significant differences in the histoarchitecture and morphology of the liver cells of the albino rats in the experimental groups when compared to the control group. The final result was necrosis of the hepatocytes in 4 weeks of drug administration of 2.1mg/KgBw and 2.8mg/KgBw degeneration and inflammation of the hepatocytes increased simultaneously with drug dosage and timing in weeks.
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1. Introduction

The liver is the processing center of the major metabolic activities in vertebrates and should be considered in terms of absorption of foreign materials such as foods, drugs etc to ascertain its high functional status (Garrelt and Grisham, 1999; Oforibika and Ezekiel, 2017).

Most manifestation of liver dysfunction stem from cell damage and death of hepatocytes. In this case manifestation may include increased bleeding due to decreased synthesis of clothing factors, jaundice and increased levels of circulating hepatocytes enzymes released from death liver cells. Hence, the effect of Zidovudine on liver histology is an important biochemical index of liver function that should not be overlooked.

This is to ensure that liver function is not impaired in the process of managing a particular health problem which in case of HIV patients is hoping to reduce the replication of the virus in the human system, while, a lot of damage is being done to the liver by these same drugs. This research would provide appropriate information required for effective life management and coping strategies during the process.

2. Material and Methods

2.1 Drug Source

Antiretroviral drug sample is used in this study. Zidovudine was purchased from Barata Pharmaceutical Store which is NAFDAC approved located at Rumuokuta junction along Ikwerre Road.

Nevran 300mg (manufactured by Ranbaxy Loboratories Ltd, Paonta Sahib, District Sirmour, Batch No. 235536, MDF 1/2/2011, Exp. 11/2013, NAFDAC Reg. No. 04-2708. Specimen (animal) used for the experiment. Sixty three (63) albino rats were purchased from the Department of Human Psychology, University of Nigeria.

Enugu Campus (UNEC) and acclimatized for one week at the animal house of Biochemistry department, University of Port Harcourt located at the botanical garden, Choba Park.

During acclimatization, the animals were fed with rat pellets and water and libiutum. Experimental procedures involving the animals and their care were conducted in conformity with international national and institutional guidelines for the care of laboratory animals in biomedical research promulgated by the Canadian Council of Animal Care.

2.2 Animal Sacrifice

Animals were sacrificed 24 hours after the last treatment, the rates were at the time of sacrifice first

weighed and then cervical dislocation was carried out in the abdominal cavity of each rat was opened up through a midline abdominal incision. The animals were dissected and only the liver collected for histopathological studies.

2.3 Histological Procedures and Analysis

This was done as described by Ogunlade *et al.* (2008). Briefly the liver was cut on slabs about 0.5cm thick and fixed in 10% Normal saline for a day after which they were transferred to 70% alcohol for dehydration.

The tissues were passed through 90% alcohol and chloroform for different durations before they were transferred into two changes of molten paraffin wax for 20mins each in an oven at 57^{o}C.

Several sections of 5µm thick were obtained from a solid block of tissue and were stained with haematoxylin and esoim stating after which they were passed through a mixture of equal concentration of xylene and alcohol, following clearance xylene, the tissues were oven dried.

Photomicrographs were taken with a JVC colour video digital camera (JVC China) mounted on an Olympus light microscope (Olumpus UK Ltd, Essex, UK) to demonstrate cytoarchitecture of the liver.

3. Results

In this research it was observed that duration and concentration of drug administered to the Albino rats produce a marked alteration in the architecture of liver morphology.

The representative sector of the control showed normal morphology (GROUP A). In Group B of 0.7mg/KgBw of drug administration in weeks 1 and normal morphology, week 2 mild hepatocyte change while week 3 mild inflammation and week 4 mild inflammation changes.

In Group C of 1.4mg/KgBw week 1 shows normal morphology; week 2 cytoplasmic degeneration, week 3 hepatocyte sinusoidal dilation while week 4 inflammatory cells. In Group D of 2.1mg/KgBw, week 1 shows hepatic sinusoidal dilation, week 2 hepatocyte degeneration while 3 and 4 show hepatocyte necrosis. In Group E of 2.8mg/KgBw, week 1 drug administration to the rats shows vascular degeneration, week 2 inflammation and fatty degeneration while week 3 shows hepatocyte degeneration and week 4 hepatocyte necrosis.

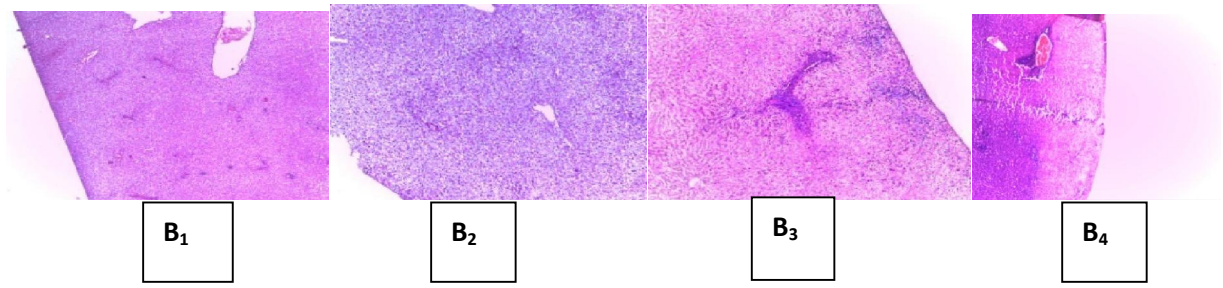


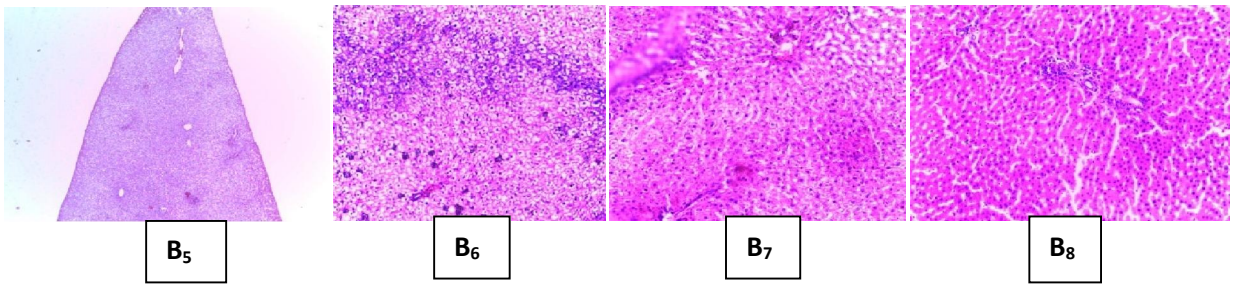
Plate 2: Photomicrograph (100X) of liver tissues treated with zidovudine for 4 weeks (H & E)

B$_1$: Photomicrograph of liver tissues at week1 of 0.7mg/Kgbw treated with zidovudine showed normal morphology.

B$_2$: Photomicrograph of liver tissues at week2 of 0.7mg/Kgbw treated with zidovudine showed mild hepatocyte change.

B3: Photomicrograph of liver tissues at week3 of 0.7mg/Kgbw treated with zidovudine showed mild inflammation.

B4: Photomicrograph of liver tissues at week4 of 0.7mg/Kgbw treated with zidovudine showed mild inflammatory change.

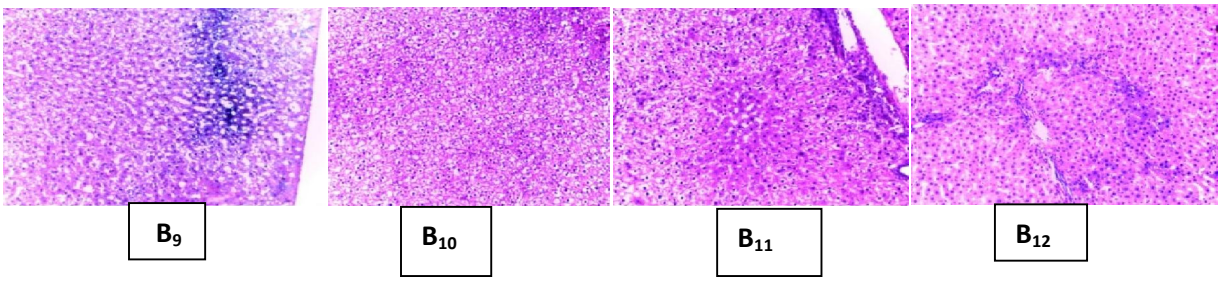


B_5: Photomicrograph of liver tissues at week1 of 1.4mg/Kgbw treated with zidovudine showed normal morphology.

B_6: Photomicrograph of liver tissues at week2 of 1.4mg/Kgbw treated with zidovudine showed cytoplasmic degeneration.

B_7: Photomicrograph of liver tissues at week3 of 1.4mg/Kgbw treated with zidovudine showed hepatic sinusoidal dilation.

B_8: Photomicrograph of liver tissues at week4 of 1.4mg/Kgbw treated with zidovudine showed inflammatory cells.

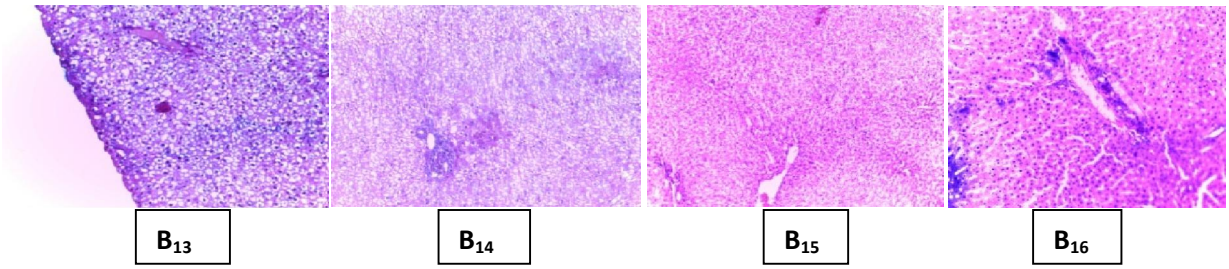


B_9: Photomicrograph of liver tissues at week1 of 2.1mg/Kgbw treated with zidovudine showed hepatic sinusoidal dilation.

B_{10}: Photomicrograph of liver tissues at week2 of 2.1mg/Kgbw treated with zidovudine showed hepatocyte degeneration.

B_{11}: Photomicrograph of liver tissues at week3 of 2.1mg/Kgbw treated with zidovudine showed hepatocytes necrosis.

B_{12}: Photomicrograph of liver tissues at week4 of 2.1mg/Kgbw treated with zidovudine showed hepatocytes necrosis.

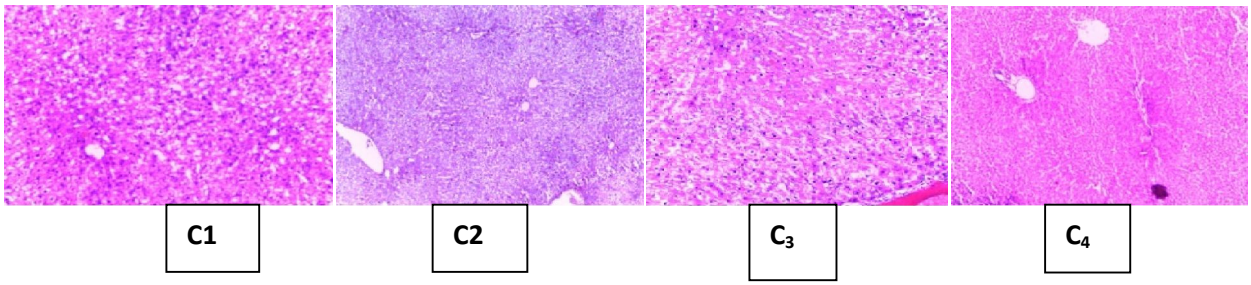


B_{13}: Photomicrograph of liver tissues of week1 of 2.8mg/Kgbw treated with zidovudine showed vacoular degeneration.

B_{14}: Photomicrograph of liver tissues of week2 of 2.8mg/Kgbw treated with zidovudine showed inflammation and fatty degeneration.

B_{15}: Photomicrograph of liver tissues of week3 of 2.8mg/Kgbw treated with zidovudine showed hepatocyte degeneration.

B_{16}: Photomicrograph of liver tissues of week4 of 2.8mg/Kgbw treated with zidovudine showed hepatocyte necrosis.



4. Discussion

The histopathological assessment of liver was carried out in all the rats in Group A (Control), B, C, D and E. Four different concentrations of the drug were administered to the experimental animals in the four groups except the control group.

Result shows morphological and histological changes in the hepatocytes when compared to the control group in all concentrations of drugs administered in all the weeks except week 1 of 1.7mg/KgBw that shows normal morphology since hepatotoxicity has been reported for all antiretroviral

classes nevirapine attributed the highest risk followed by Zidovudine among the first generation drugs while Lamivudine has been least reported in previous works and that of Suikwoski *et al.* (2000). But this work has reported hepatic sinusoidal dilation and hepatocytes necrosis at different drug concentration and duration.

Drug associated hepatotoxicity also creates an economic burden on already strained medical budgets, since additional visits and hospital admissions are often required for appropriate patient care and management (Nunez *et al.,* 2006).

Furthermore, antiretroviral drug discontinuation hampers maintenance of HIV suppression. The seventy of ARLI may range from the absence of symptoms to liver decompensation and the outcome can range from spontaneous resolution to liver failure and death (Clark *et al.,* 2002).

Several highly active antiretroviral therapy (HAART) regimens are hepatotoxic and the liver is one of the vital organs useful in the metabolism of the drugs as well as in detoxification.

It is therefore important that the liver which is the main biochemical hub of the body be monitored and those HAART regimens that may be toxic to it be identified so that modification or replacement can be made to enhance patient's care.

5. Conclusion

In conclusion, within limits of experimental error, this research work have demonstrated that antiretroviral treatment with Zidovudine may be associated with liver inflammation and degeneration of the hepatcytes and finally in hepatocyte necrosis.

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