Hepatotoxicity of Lamivudine on the Liver

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Abstract: Hepatotoxic effects of antiretroviral drugs Lamivudine on Wister Albino rats were investigated using histopathological studies of the liver. A total of 63 Albino rats of weight range (124 – 197) 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 experimental groups which are orally treated with 4 different doses (0.7mg/KgBw, 1.4 mg/KgBw, 2.1 mg/KgBw, 2.8 mg/KgBw) respectively four 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 Lamivudine produce significant differences in the histoarchitecture and morphology of the liver cells of the albino rats in the treatment group when compared to the control group. The result of these was necrosis of the liver in the 4th week of 2.8mg/KgBw and 2.1mg/KgBw. Degeneration and inflammation of the hepatocytes increased simultaneously with drug dosage and timing.

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1. Introduction

Hepatotoxicity is a serious problem especially on those that have been on highly active antiretroviral therapy limiting the regimen. Drug induced toxicity is the most frequent reason for the withdrawal of a drug from the market and accounts for more than 50% of cases of acute liver failure in the United States.

The exact mechanism by which Lamivudine case adverse hepatic effect have not been elucidated but Lee (2008), reported that drug induced liver injury occurs via at least six (6) mechanisms involving various intracellular organelles, with consequent disruption of intracellular calcium homeostasis, decline ATP levels and finally hepatocyte swelling and repture (Yun *et al*., 1993). A damaged liver may fail to metabolise drugs and thus prolong their stay in circulation and cause further toxicity or drugs that need to be metabolized to active firms may not be so converted hence the patient mail to comply with treatment regimen both of which may adversely affect the outcome of treatment. The aim of this work was to assess the level of lamivudine toxicity in liver histology.

Lamivudine is associated with hepatic adverse in effect in this study and therefore must be used with caution alongside with close monitoring of liver enzymes which was carried out in one of our research but was not reported here. The paper advocated for inclusion of treatment regimen of agents which are hepato-protective.

2 Materials And Methods

2.1 Drug Source

Antiretroviral drug sample is used in this study. Lamivudine 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 (17).

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 Analysis

This was done as described by Ogunlade *et al.,* (18). 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 panaflix 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 And Discusion

3.1 Results

The histopathological assessment of liver was performed for all the rats in Group A (control), B, C, D, and E. The highest dose was administered in Group E in all the weeks. The treated groups shows histological and morphological changes when compared to the control in each week of the Albino rats administered with Lamivudine.

In Group B week 1 at 0.7mg/KgBw of the drug Lamivudine shows normal morphology while week 4 showed inflammatory change. In group C (1.4mg/KgBw) of the drug lamiductive week 1 and 2 dows mild distortion of hepatcytes, week (2) cytoplasmic degeneration while week 3 and week 4 shows fatty change and mild inflammatory change respectively.

In Group D of 2.1mg/KgBw drug administration in week 1 shows vascular degeneration of hepatocytes, week 2 degeneration of cytoplasm. Week 3 zone 3 hepatocyte necrosis and week 4 hepatocyte necrosis respectively.

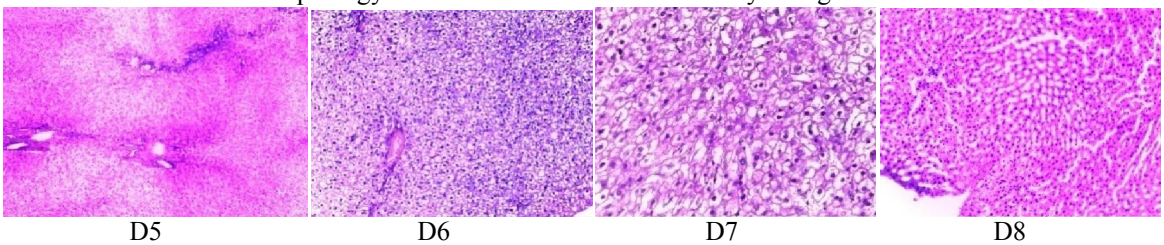
In Group E of 2.8mg/Kgbw drug administration in week 1 shows hepatocyte cytoplasmic degeneration, week 2 cytoplasmic degeneration and hepatocyte distortion. While in week 3 and week 4 out gave nepatocyte necrosis respectively as seen in the photomicrograph of liver issues. Plates 4.4 photomicrograph (100x) of liver tissues treated with lamivudine for 4 weeks (H & E).

D_1: Photomicrograph of liver tissues at week 1 of 0.7mg/Kgbw treated with lamivudine showed normal morphology.

D_2: Photomicrograph of liver tissue at week 2 of 0.7mg/Kgbw treated with lamivudine showed normal morphology.

D_3: Photomicrograph of liver tissues at week3 of 0.7mg/Kgbw treated with lamivudine showed normal morphology.

D_4: Photomicrograph of liver tissues at week4 of 0.7mg/Kgbw treated with lamivudine showed inflammatory change.



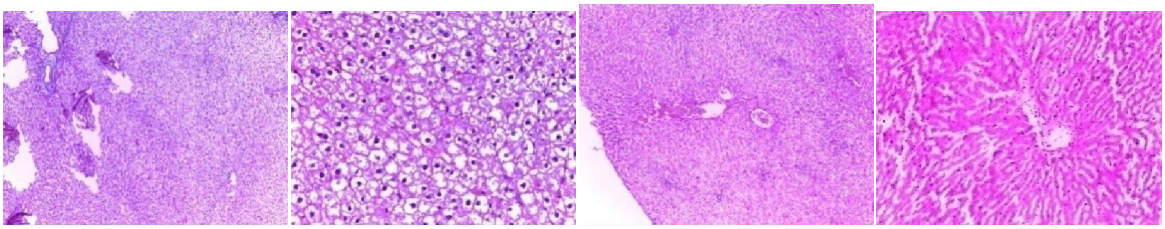
D5 D6 D7 D8

D_5: Photomicrograph of liver tissues at week1 of 1.4mg/Kgbw treated with lamivudine showed mild distortion of hepatocytes.

D_6: Photomicrograph of liver tissues at week2 of 1.4mg/Kgbw treated with lamivudine showed cytoplasmic degeneration.

D_7: Photomicrograph of liver tissues at week3 of 1.4mg/Kgbw treated with lamivudine showed fatty change.

D_8: Photomicrograph of liver tissues at week4 of 1.4mg/Kgbw treated with lamivudine showed mild inflammatory changes.

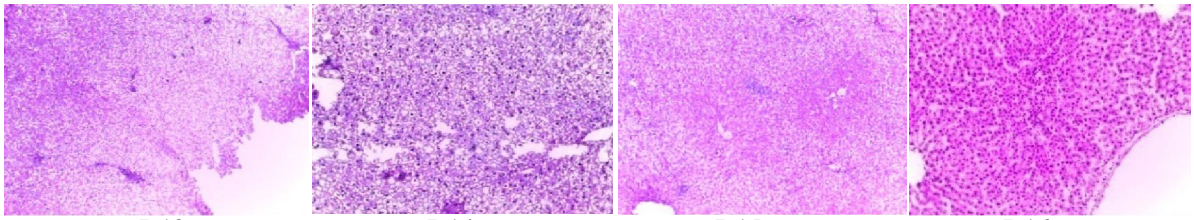


D9 D10 D11 D12

D_9: Photomicrograph of liver tissues at week1 of 2.1mg/Kgbw treated with lamivudine showed vacoular degeneration of hepatocytes.
D_{10}: Photomicrograph of liver tissues at week2 of 2.1mg/Kgbw treated with lamivudine showed degeneration of cytoplasm.

D_{11}: Photomicrograph of liver tissues at week3 of 2.1mg/Kgbw treated with lamivudine showed zone3 hepatocyte necrosis.

D_{12}: Photomicrograph of liver tissues at week4 of 2.1mg/Kgbw treated with lamivudine showed hepatocyte necrosis.



D13 D14 D15 D16

D_{13}: Photomicrograph of liver tissues of week1 of 2.8mg/Kgbw treated with lamivudine showed hepatocyte cytoplasmic degeneration.
D_{14}: Photomicrograph of liver tissues of week2 of 2.8mg/Kgbw treated with lamivudine showed cytoplasmic degeneration and hepatocyte distortion.
D_{15}: Photomicrograph of liver tissues of week3 of 2.8mg/Kgbw treated with lamivudine showed hepatocyte necrosis.
D_{16}: Photomicrograph of liver tissues of week4 of 2.8mg/Kgbw D treated with lamivudine showed hepatocyte necrosis.

Discussion

The histopathological assessment of the liver was performed for all the rats in Groups A, B, C, D and E. The lowest dose was administered in B in all the weeks while the control groups are administered with no drug. The experimental groups show histoarchitectural and morphological changes when compared to the control group in all the weeks as shown in the histology diagram.

However, in all the weeks of drugs administration from 1.4mg/KgBw to the highest dose of 2.4mg/KgBw distortion of liver morphology to necrosis of the hepatocytes was observed in those study.

Although Hepatotoxicity has been reported for all antiretroviral classes, nevirapine was attributed the highest risk but Lamivudine has been least reported (Sulkwoski *et al*., 2000; Reister, *et al*., 2001). But out study has encountered distortion of liver morphology and necrosis of the hepatocytes. Administration of drugs that are hepatotoxic to HIV/AIDS patients may have untoward consequences. The lives of patients are put at risk. A damage liver may fail to metabolize drugs and thus prolong their stay in circulation and cause further toxicity or drugs that need to be metabolized to active forms may not be converted.

There is high chance that a drug may be withdrawn due to its toxicity (Sule, *et al*., 2012). We advocate for the use of dietary and medicinal prevention or treatment of liver disease by plant based stuffs as an essential constituent of complementary and alternative medicine (Dudhatra *et al.,* 2012).

Liver protective fruits, as well as plants contain a variety of chemical compounds such as phenols, caumarins, lignans, essential oils, monoterpenes, glycosides, alkaloids, carotenoids, flavononoids, organic acids and xanthenes (Gupta, *et al.,* 2011).

Hepatoprotective plants foods from wild and semidomesticated origin should be added to the diet of HIV/AIDS patients and these include: buck wheat, celery, capillary wormwood, chest nut, heart lead, longstamen onion bulb, lotus roof, olive, red date, and tangerine.

Conclusion

With the limits of experimental error, the research work has demonstrated histological and morphological changes of the liver as the drug dosage and timing increases degeneration and inflammation of the hepatocytes increases causing necrosis of the liver. In conclusion, it can be deduced that Lamivudine regimen should be safely administered alongside with hepatoprotective. The treatment regimen of agents which are hepatoprotective should be seriously considered.

Recommendations

We recommend that lamivudine based regimen may be safely initiated to those of lower risk unless the benefit clearly outweighs the risk.

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