Hepatotoxicity Of Nevirapine On The Liver

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Abstract: The study was conducted to investigate the histopathological effect of the highly active antiretroviral drug nevirapine administration on liver histology. A total of 63 albino rats of weight range (124-197g) were divided into 5 groups (n = 5) labeled A, B, C, D, and E. Group A served as control treated with only distilled water, while groups B, C, D, E were orally treated with different doses (0.7mg/kgBw, 1.4mg/kgBw, 2.1mg/kgBw and 2.8mg/kgBw) respectively for four weeks. Animals were sacrificed weekly and histological examination of the liver for four 4 weeks was carried out. Results obtained revealed that the administration of the four different drug concentrations of Nevirapine on the ra produces significant difference on the histoarchitecture and morphology of the liver cell when compared to the control group. As the drug dosage and timing increases degeneration and inflammation of the hepatocytes increases causing necrosis of the liver in the 4th weeks of 2.1mg/kgBw and 2.8mg/kgBw administration of the drug. From the study it can be concluded that Nevirapine administration has obvious gross deterious effect on liver morphology.
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1. Introduction

Hepatotoxicity is one of the most serious complications of highly active antiretroviral drugs. The aim of this report is to analysis the effect of Nevirapine toxicity on the liver. Hepatotoxicity has been reported among all antiretroviral classes and Nevirapine has been attributed to be the highest risk (Sulkwosky *et al.,* 2001, Reislere, *et al.,* 2002).

Nevirapine is a non nucleoside reverse transcriptase inhibitor (NNRTs) which is often used in HAART regiments and it binds allosterically at a distinct site away from the active site termed the NNRTU pocket (Bartielt *et al.,* 2003). However, increasing reports of adverse clinical events have diminished the enthusiasm generated by Nevirapine. The most common adverse effect encountered is cusaneous rash, post inflammatory changes and fatty liver tissue has been observed. Nevirapine has shown to cause severe or life threatening liver toxicity usually emerging in the first few weeks of treatment as seen in this work and also it was reported in the report of DHHS Panel 2006, Wit, 2008).

However, some clinical trials have demonstrated comparable HIV suppression with Nevran based regimen to that achieved with protein inhibitors (PTS) (Van Leeuwen *et al.,* 2003). Although concerns have been raised about nevran based regiments in those starting therapy or low CD^4 count (Lethal *et al.,* 2005).

In another study it was reported that Nevirapin may also form a useful component of salvage regimen after virological failure, usually in combination with one or more PIS as well as NRTIs, especially in those who have not previously taken an NNRTI.

African effort on the safety of Nevran is not fully elucidated. Since the liver is one of the vital organs useful in the metabolism of these drugs (including Lamivudine) as well as in detoxification (Oforibika and Ezekiel, 2017).

It is therefore necessary that the liver, which is the main biochemical hub of the body be monitored and these ART regimens that may be toxic be identified so that changes or modifications can be made in order to enhance adequate management and patient care.

2. Material And Methods

2.1 Drug Source

Antiretroviral drug sample is used in this study. Neviripine 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

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 57ºC.

Several sections of 5µm thick were obtained from a solid block of tissue and were stained with haematoxylin and esoim staining after which they were passed through a mixture of equal concentration of xylene and alcohols, 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.

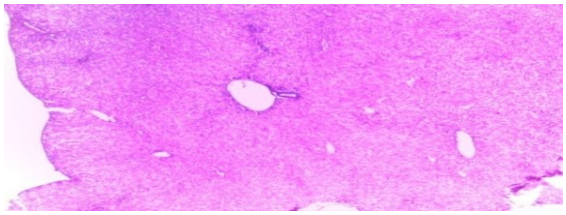
3. Results

3.1 Hispathology of liver Results

In these results, there were significant changes between the experimental groups and the control group. It was observed that quality and duration of Nevran.

Consumption by the albino rats produced a marked alteration in the histoarchitecture of liver morphology. The representative section of the control showed normal morphology (Figure A). In week 1 and 2 of Group B at 0.7mg/KgBw of the drug Nevran administration on the rats shows an initial mild fatty change and mild hepatocytes degeneration while in Week 3 and 4 cytoplasmic and hepatocyte degeneration was observed and in group C that was given 1.4mg/KgBw, in week 1 and 2 cytoplasmic degeneration inflammatory changes of the hepatocytes was observed while in Week 3 fatty change and hepatocyte disarray was observed and Week 4 inflammatory change.

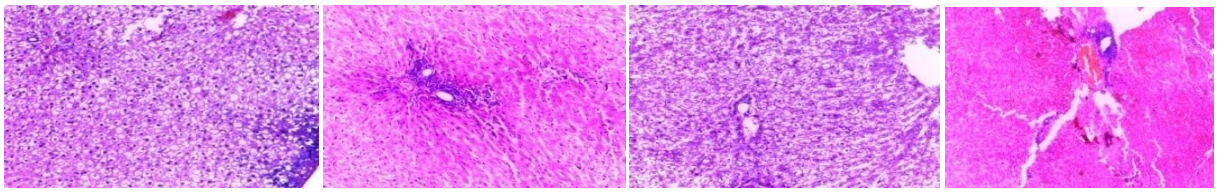
In group D 2.1mg/KgBw in Week 1 and Week 2 hepatocyte degeneration and mild fatty change while in Wee 3 and 4 necrosis of the hepatocytes was observed. In group E with the highest drug concentration of (2.8mg/KgBw) Week 1 and Week 2 recorded hepatocyte degerenation and cytoplasmic degeneration while in Week 3 hepatoxyte generation and necrosis was observed and Week 4 recorded necrosis of the hepatocytes.



A

Plate 1: Photomicrograph (100X) liver tissues treated with distilled water (H & E).

A: Photomicrograph (100x) liver tissues from the control group (distilled water treated group) showed normal morphology.



C_5 **C_6** **C_7** **C_8**

Plates 2: Photomicrograph (100X) of liver tissues treated with nevirapine for 4 weeks (H & E).

B_1: Photomicrograph of liver tissues at week1 of 0.7mg/Kgbw treated with nevran showed mild fatty tissue.

B_2: Photomicrograph of liver tissues at week2 of 0.7mg/Kgbw treated with nevran showed mild hepatocyte degeneration.

B_3: Photomicrograph of liver tissues at week3 of 0.7mg/Kgbw treated with nevran showed cytoplasmic and hepatocyte degeneration.

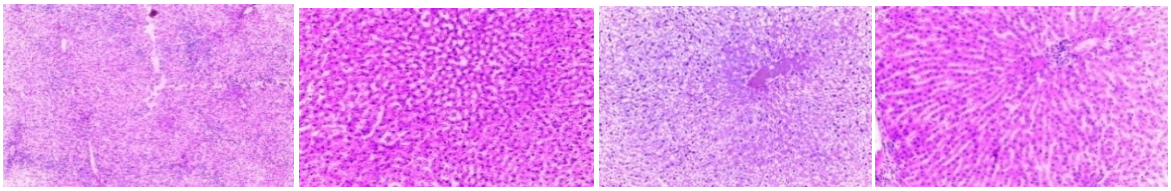
B4: Photomicrograph of liver tissues at week4 of 0.7mg/Kgbw treated with nevran showed cytoplasmic and hepatocyte degeneration.

C_1: Photomicrograph of liver tissues at week1 of 1.4mg/Kgbw treated with nevran showed cytoplasmic degeneration of hepatocytes.

C_2: Photomicrograph of liver tissues at week2 of 1.4mg/Kgbw treated with nevran showed inflammatory change.

C_3: Photomicrograph of liver tissues at week3 of 1.4mg/Kgbw treated with nevran showed fatty change and hepatocyte disarray.

C_4: Photomicrograph of liver tissues at week4 of 1.4mg/Kgbw treated with nevran showed mild inflammatory change.



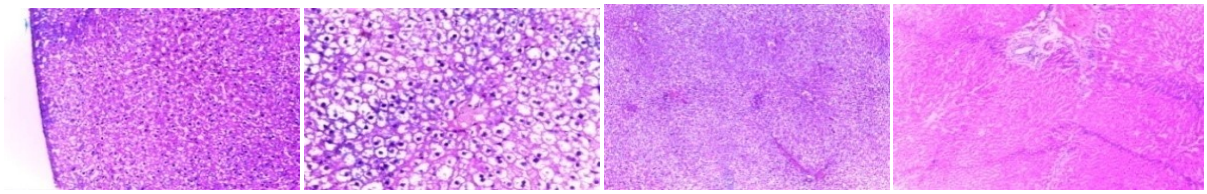
C_5 **C_6** **C_7** **C_8**

D_1: Photomicrograph of liver tissues at week1 of 2.1mg/Kgbw treated with nevran showed hepatocyte degeneration.

D_2: Photomicrograph of liver tissues at week2 of 2.1mg/Kgbw treated with nevran showed mild fatty change.

D_e: Photomicrograph of liver tissues at week3 of 2.1mg/Kgbw treated with nevran showed hepatocyte necrosis.

D_4: Photomicrograph of liver tissues at week4 of 2.1mg/Kgbw treated with nevran showed hepatocyte necrosis.



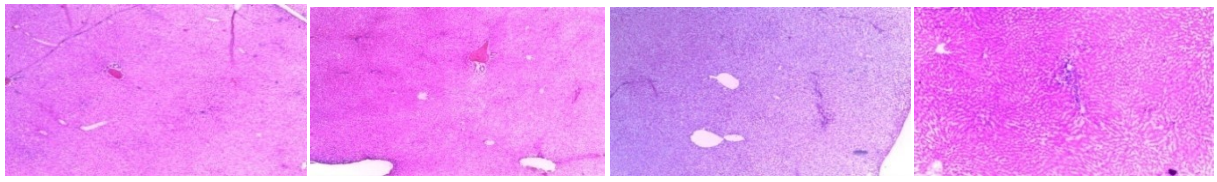
C_5 **C_6** **C_7** **C_8**

E_1: Photomicrograph of liver tissues of week1 of 2.8mg/Kgbw treated with nevran showed hepatocyte degeneration.

E_2: Photomicrograph of liver tissues of week2 of 2.8mg/Kgbw treated with nevran showed cytoplasmic degeneration.

E_3: Photomicrograph of liver tissues of week3 of 2.8mg/Kgbw treated with nevran showed hepatocyte degeneration and necrosis.

E_4: Photomicrograph of liver tissues of week4 of 2.8mg/Kgbw treated with nevran showed hepatocyte necrosis.



D1 **D2** **D3** **D4**

4. Discussion

The histopathological assessment of the liver was performed for all the rats in Group A (Control), B, C, D, and E.

The highest dose (2.8mg/KgBw) was administered in Croup E in all the weeks. The treated groups show histological and morphological changes when compared to the control in each week in the histology diagram. However in this work, all the weeks of 2.8mg of Nevran administration the liver of the entire rat showed hepatocytes degeneration and necrosis of the hepatocytes.

Lucien *et al.*, (2008) opined that long term use of Nevran (NNRT) can cause life threatening liver problems. Most importantly, in both animals and humans relating to biochemical changes caused by drugs, histopathological study of the liver can be used as an index to assess the rate of drug induced liver injury as seen in this work and others (Aktar *et a.,* 2008).

Studies carried out by the U.S. Food and Drug Administration in 2000 causes the issuing of a black box label on Nevirapin, warning that it could cause severe liver damage, including liver failure. Nevran has been showed to cause severe life threatening liver toxicity, usually emerging in the first weeks of the treatment (DHH Wit, 2008).

Unacceptably high risk of serious liver symptoms in certain patient groups (women with CD4 count >250 and men >400) has led to the US DHSS to recommend the use of Nevran to those at lower risk unless the benefit to the patient clearly outweighs the risk (CDHHS Panel 2006, Sule *et al.,* 2003).

Despite enormous advances in modern medicine, there are no completely effective drugs that stimulate hepatic function that office complete protection of the organ or that help to regenerate heptic cells (Chattapadhyay, R.R., 2003).

The use of fruits have played basic role inhuman health care and diverse scientific investigations have indicated that in these plants and fruits, their beneficial effects can be attributed to the presence, of chemical compounds that are called phytochemicals.

Those plants and fruits have demonstrated hepatoprotective capacity. While many more are claimed to be hepatoprotective but lack any such scientific evidence to support such claims.

Developing a satisfactory herbal therapy to treat severe liver disease requires systematic investigation of properties like anti-hepatotoxicity (antioxidants) stimulation of liver regeneration and choleretic activities (Arafa Shaik *et al,* 2012).

Foods rich in natural antioxidants have been proposed as a tool to prevent and cure liver damage (Morisco, *et al.,* 2008). Hepatoprotective plant foods from wild and semidomesticated origin consist of Amaranth, Aralia elata seem, asparagus, ballon flower root (platycodon grandiflorus), buok wheat, celery, capillary wormwood, chest nut, heart leaf, lonstamen onion bulb, lotus root, mango, papaya, etc (Martin C. *et al.,* 2013).

As seen in these results and from various earlier reports on related studies, it could be concluded that the lives of HIV patients on regular use of HAART, containing Nevirapine are put to risk. Similar case of lives failure as a consequent of Nevirapine toxicity was reported by Anonymous (2000) and Bartiett and Gallant (2003) and Sule, O. J. *et al.,* (2012).

4.1 Conclusion

Within the limits of experimental error, this research work has demonstrated that the use of Nevripine has an adverse effect on the histology of the liver even at minimal dose. In this work hepatocytes degeneration and necrosis of the hepatocytes was observed at the highest dose.

4.2 Recommendations

The study suggests that Nevran based combination therapy may be safely initiated in patient. In our findings it was the experimental animals that received the highest dose that showed hepatocytes generation and necrosis of the hepatocytes.

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