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Effect Of Efavirenz on the Histo-architecture of the Liver of Wistar Rats

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ABSTRACT

For HIV positive people, the liver is of major importance, as it processes many of the drugs used to treat HIV and AIDS related infections. These same medications can also damage the liver and can prevent it from performing all its necessary functions. This study was carried out to determine the effects of the antiretroviral drug, Efavirenz on the histo-architecture of the liver of albino rats. A total of thirty albino rats were used for the experiment and were randomly divided into five groups of six rats each. Rats in group A served as control and were not administered the drug while rats in test groups B, C, D, and E received varying doses of Efavirenz which were 150mg, 180mg, 210mg and 230mg respectively. Two rats each from each group were sacrificed at the end of week one, two and three respectively. Liver tissues were harvested and preserved with 10% formalin, processed and stained for light microscopy. Result showed normal histological features for the control. Efavirenz did not distort the histo-architecture of groups B, C, and D at the end of the first and second weeks. However, mild liver necroses were observed in groups D and E at the end of week three. Results obtained shows that the effects of Efavirenz on the liver increases with increasing dosage and duration of exposure.

Key words: Efavirenz, liver, necrosis.

Efavirenz (EFV, brand names Sustiva and Stocrin) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1. Efavirenz is a noncompetitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. Efavirenz is chemically described as (S)-6-chloro-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one. Its empirical formula is $C_{14}H_9ClF_3NO_2$. Efavirenz is a yellow coloured, oval shaped biconvex film coated tablets, deposed with "D" on one side and "37 "on the other side, (Ren *et al* 2002).The tablet core is made up of crystalline cellulose, sodium lauryl sulphate, croscarmellose sodium, hydroxypropyl cellulose lactase monohydrate and magnesium stearate. Film coat; hypromellose, titanium dioxide, polyethlene glycol and yellow iron oxide (WHOPAR, 2010). Each film coated tablet of Efavirenz contains 600mg, and is usually taken by adults once a day with an empty stomach at bed time to reduce neurological and psychiatric adverse effects.

For HIV-positive people, the liver is of major importance, as it is responsible for making new proteins needed by the immune system, helps the body to resist infection, and processes many of the drugs used to treat HIV and AIDS-related infections (Koutsavlis *et al*, 2005; Pozniak, 2006). Unfortunately, these same medications can also damage the liver, and can prevent the liver from performing all of its necessary tasks.

Hepatic side effects of efavirenz have included elevated AST (greater than 180 units/L in males and 170 units/L in females; 3%) and ALT (greater than 215 units/L in males and 170 units/L in females; 2%). Elevated bilirubin (greater than 2.5 times ULN) has been reported in up to 3% of patients treated with emtricitabine or tenofovir (Starr *et al* 1999). Hepatic enzymes increase, hepatic failure (a few reports were characterized by a fulminant course, with some cases progressing to transplantation or death), and hepatitis have been reported during post-marketing experience with Efavirenz. Hepatic steatosis, hepatitis, and increased liver enzymes (primarily AST, ALT, and gamma glutamyl transferase) have also been reported during post-marketing experience with efavirenz (Gallant *et al* 2005)

Some of the post-marketing reports of hepatic failure with Efavirenz occurred in patients with no pre-existing liver disease or other identifiable risk factors. Increased levels

of liver enzymes have been reported in some Efavirenz users. In some cases, this may be an indicator of liver damage (Antinori, 2007).
The aim of this study therefore, is to determine the effects of Efavirenz on histo-architecture of the liver of albino wistar rats.

MATERIALS AND METHODS

Thirty (30) albino wistar rats (male and female) were recruited from an animal farm in Enugu state, with weight ranging from 100 to 175g. The rats were administered with Efavirenz, and studied prospectively over a period of three weeks under normal laboratory conditions, in the histology laboratory of the University of Port Harcourt, with a temperature of C and with artificial lightening (12hours dark and 12 hours light). They were placed in plastic cages bedded with saw dust, covered with metal netting, fed with pelletized grower feed and water for seven (7) days for acclimatization.

The animals were divided into five (5) groups of six (6) experimental animals; group A (control), group B fed with 150mg of Efavirenz for, Group B were administered with 180mg of Efavirenz orally, Group C; fed with 210mg of efavirenz, Group D; had 150mg of efavirenz tablet while group D; had 230mg of efavirenz. Males were separated from females.

The test doses were chosen after the determination of LD_{50} using the acute oral toxicity-up-and-down procedure and was found to be greater than 5000mg/kg.

Histological Study:

Liver tissues collected were fixed in 10% formalin for 24 hours and thereafter processed for paraffin wax sectioning at 4 micron and stained with Hematoxylin and Eosin. The slides were examined under a light microscope using magnification and pathological evaluation was done by a pathologist in the department of Anatomical pathology of the University of Port-Harcourt Teaching Hospital who was blind to the nature of the study.

RESULTS

Results showed control group with normal hepatic histology. The experimental groups showed considerable variations in the hepatic histo-architecture. While test groups B,C,D and E showed no abnormality in histo-architecture of the liver in weeks 1 and 2, groups D (female) and group E (both male and female) showed mild liver necrosis in week 3 as shown in photoplates1-3 below. Macro-observation showed pseudo membranous inflammation of the liver in week 3.

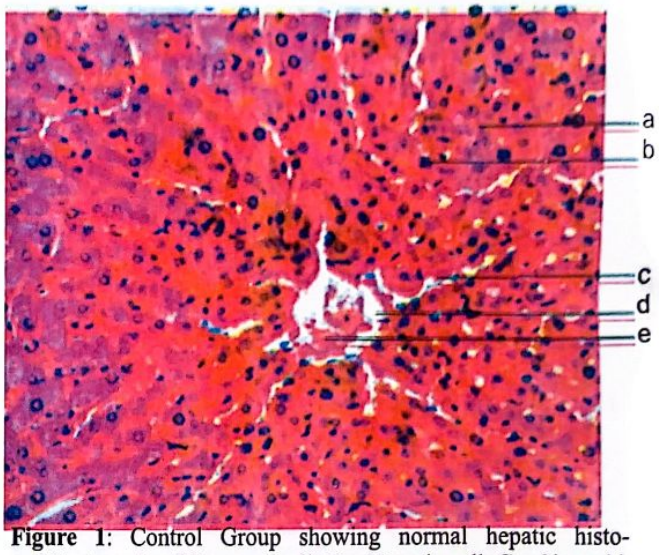

Figure 1: Control Group showing normal hepatic histo-architecture. A = Bile canaliculi, B = Hepatic cell, C = Sinusoid, D = Hepatic venule, E = Central vein.

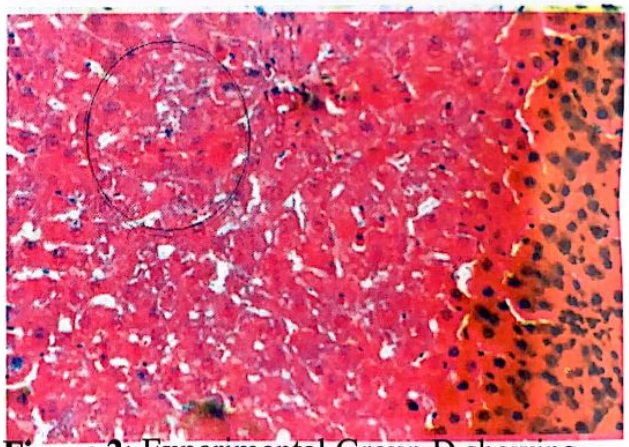

Figure 2: Experimental Group D showing sections of mild hepatic necrosis.

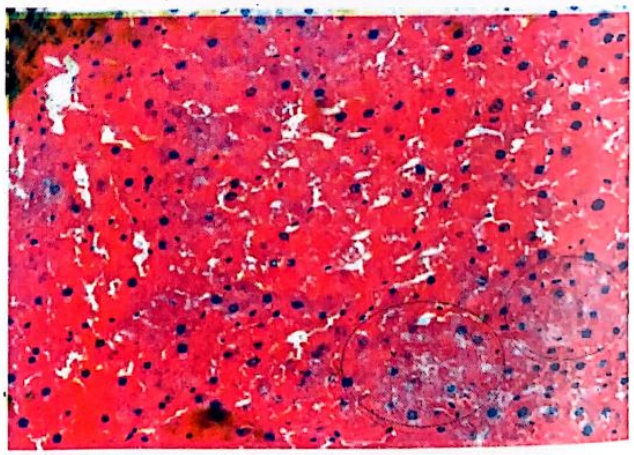

Figure 3: Experimental Group E showing sections of mild hepatic necrosis.

DISCUSSION

This study, examined the effect of the oral administration of Efavirenz, on the histo-architecture of the liver in male and female albino wistar rats. From the results, it was evident that Efavirenz did not only have an effect on the liver enzymes but also on the liver histo- architecture. Starr *et al* (1999) and Gallant *et al.*, (2005) had earlier reported increase in liver enzymes following efavirenz administration.

Macro-observations noticed pseudo membranous inflammation of the liver in week 3 and this may be as a result of congested vessels or interstitial edema in the sinusoid lining cells of the liver leading to necrosis. Inflammation is a fundamental pathologic process, consisting of a dynamic complex of histological, apparent cytological changes, cellular infiltration and mediator release that occurs in the affected blood vessels and adjacent tissues in response to an injury which could be as a result of chemical or biologic agent including the local reactions resulting morphologic changes (Stedman, 2006).

Histologically, it was observed that the photo-micrographs of test groups A-D in week 1 to week 2 (with drug doses of 150mg, 180mg, 210mg and 230mg) and groups A-C (male) in week 3 had no change in comparison to the control which showed normal histological features. In week 3 test group C (female) and test D (male and female) showed mild liver necrosis. Necrosis itself is the pathological death of one or more cells of a portion of tissues or organs resulting from irreversible damage consisting of swelling or inflammations (Stedman, 2006).

From the above definition, it can be deduced that the inflammation observed in week 3 was as a result of prolong administration of Efavirenz leading to significant hepatic tissue injury or liver necrosis. Injury or obliteration in close association with sinusoid vasculature of the liver hepatocyte causes impairment of liver function (Highleyman, 2009). From this result it was also observed that the effects of the drug on the hepatic cells were progressive and more evident as time and dose of drug administered increased. Evidence of liver damage observed in this study support that of Cameron et al, (2007).

In conclusion, Efavirenz is a less toxic antiretroviral drug in comparison to other Non-nucleoside Reverse Transcriptase inhibitors (Nevirapine and Delavirdine), but prolonged administration and at high doses could lead to liver necrosis or damage. Even though HIV drugs are intended to improve the health of HIV infected individuals, the liver recognizes these medications as toxic compounds as these drugs contain some chemicals that could potentially cause damage to the human body.

To optimize adherence and thus, efficacy of ART, clinicians must focus on preventing adverse effects whenever possible, and distinguish those that are self-limited from those that are potentially serious. Adverse drug reactions (ADRs) to antiretroviral treatment (ART) are however, major obstacles in its success.

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