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Nevirapine Causes Histopathological Changes in the Hippocampus of Wistar rats

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ABSTRACT

Nevirapine is one of the components of Duovir-N™ used for the management of human immunodeficiency virus (HIV) infection in sub-Saharan Africa. The objective of this research study was to investigate the potential harmful effects of this drug on the histology of the hippocampus of Wistar rats. Twenty male Wistar rats were used for this study. The rats were divided into 2 groups of 10 rats each. Group A served as the control, while group B were treated with 2.86 mg/kg of nevirapine twice daily for 30 days. The rats were sacrificed using chloroform inhalation method. Their hippocampus was harvested, processed and stained using the Haematoxylin and Eosin, paraffin impregnated Glial Fibrilar Acidic Protein (GFAP) and Neurofillament (NF) immunochemistry methods. Stained slides were viewed under a light microscope. Results showed that the hippocampus of Groups B animals were-affected with moderate to severe distortion of the Pyramidal and neuronal cells, when compared with the control group A. GFAP and NF test showed increased expressions in the test group B than the controls. The drug nevirapine may be harmful to the hippocampus and should be taken with caution.

Key words: Histological, nevirapine, hippocampus, Human Immunodeficiency Virus.

INTRODUCTION

Nevirapine was the first Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) approved for use in HIV-infected patients. Its efficacy has been well demonstrated in numerous clinical trials. It has activity against HIV -1 but does not have significant activity against HIV-2 or other retroviruses[1,2]. It is easy to administer and is generally well absorbed. The pharmacokinetics of nevirapine is characterized by rapid and nearly completes oral absorption, rapid distribution and prolonged elimination[3]

Nevirapine bioavailability is 90% and is not impaired by food and antacids. It is approximately 60% protein bound and achieved cerebrospinal fluid levels that are 45% of those in plasma. It has a volume of distribution of 1.21±0.09 L kg-1[4,5].

Nevirapine crosses the placenta and is reported to be secreted in breast milk. This has stimulated the use of this drug in the prevention of mother to child transmission of HIV[6]. Nevirapine mechanism of action involves binding directly to HIV-1 reverse transcriptase enzyme and causing a structural change that disrupts the formation of the active site and leads to impaired polymerization activity[7]. The urinary excretion of nevirapine is minor, since only a small fraction (<3%) is eliminated as parent compound in urine[7]. Nevirapine has been linked to some potentially serious adverse effects. One of these effects is nevirapine rash which is characterized by macular or popular eruptions commonly seen in the trunk, face and extremities. Pruritus is also associated with nevirapine. This stops when therapy is discontinued. Life threatening steven johnson's syndrome is rare but occurs[8]. Severe and fatal hepatotoxicity has been reported with nevirapine use[1,9]. Other reported side effects of nevirapine include fatigue, headache, fever, somnolence and nausea. Clinically nevirapine is typically used as a component of highly active antiretroviral regimen. In addition nevirapine have been used in the prevention of mother to child transmission of HIV.

There is dearth of literature on the effect of nevirapine on the brain. The objective of this study therefore was to investigate the effect of this drug on the histology of the hippocampus of Wistar rat.

MATERIALS AND METHODS

Twenty male Wistar rats were used for this study. The rats were divided into 2 groups of 10 rats each. Group A served as the control, while group B were administered with 2.86 mg/kg of nevirapine twice daily for 30 days. The drug was obtained from the university of Uyo Teaching Hospital pharmacy. The research was approved by the University of Uyo Postgraduate Committee. The animals were handled according to the

guidelines for the treatment of laboratory animals. The rats were treated for 30 days and allowed water and feed *ad libitum*. On the 31st th day, the rats were sacrificed using chloroform inhalation method and their hippocampus harvested, processed and stained using the Haematoxylin and Eosin, Silver impregnated method, paraffin impregnated Glial Fibrilar Acidic Protein (GFAP) and Neurofilament (NF) immunochemistry methods. Stained slides were viewed under a light microscope.

RESULTS

The histomorphological features that were present in the groups upon viewing under the light microscope were as follows.

Plate 1 (a) Showed the photomicrograph of the histology of the Hippocampus of control A with the three hippocampal layers polymorphic, pyramidal and the molecular layers, the pyramidal cells (arrow) and neuronal cells are normal. H/E X 400

Plate 1 (b) Showing the photomicrograph of the histology of the Hippocampus of group B (treated with 2.86 mg/kg of Nevirapine) showed atrophy of the pyramidal cells, and reduction in number of neuronal cells when compared with the control Silver Staining X 400

Plate (II a) showed the photomicrograph of the histology of the Hippocampus of control A with the three hippocampal layers polymorphic, pyramidal and the molecular layers, the pyramidal cells (arrowed) and neuronal cells appear normal. Silver Stain X 400.

Plate II (b) Photomicrograph of the histology of the Hippocampus of group B treated with 2.86mg/kg of Nevirapine showed atrophy of pyramidal cells and smaller neuronal cells when compared with the control Silver Stain X 400

Plate IIIa Photomicrograph of the histology of the Hippocampus of control administered with 1.00 ml of distil water showed normal expression of GFAP by astrocytes (arrow).

Plate IIIb Photomicrograph of the histology of the Hippocampus of group B treated with 2.86mg/kg of Nevirapine showed increased expression of GFAP by astrocytes (arrow) in group B treated with Nevirapine than the control group GFAP X 400

Plate IVa. Photomicrograph of the histology of the Hippocampus of group A treated with 1 .00 ml of distill water showed normal expression of NF (arrows) NF X 400

Plate IVb Photomicrograph of the histology of the Hippocampus of group B treated with 2.86mg/kg of Nevirapine showed increased expression of NF (arrows) and more cellular population stained in group B treated with Nevirapine than the control group NF X 400

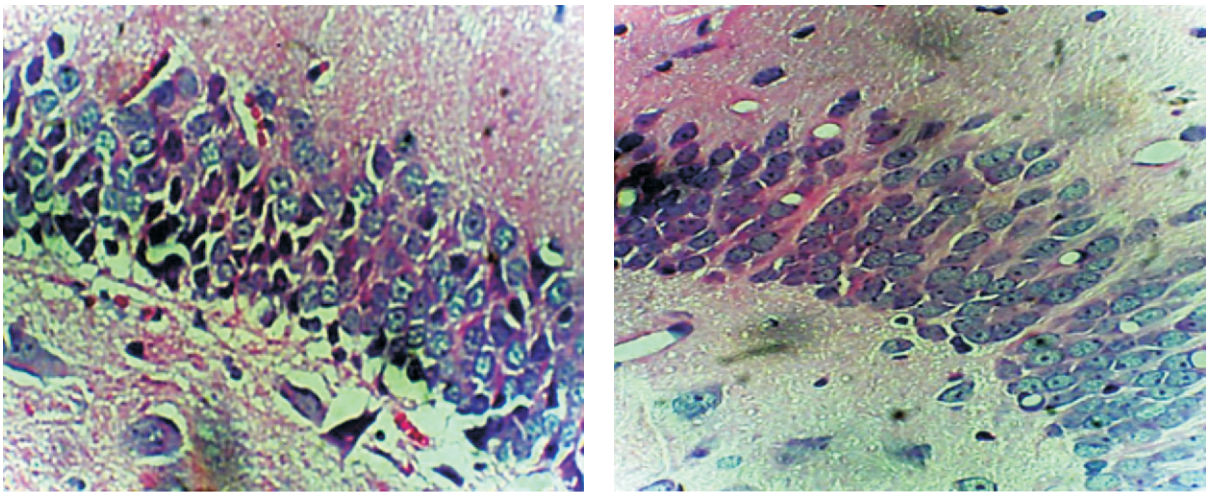

Plate Ia and 1b Photomicrograph of the histology of the Hippocampus of control A and group B (treated with 2.86 mg/kg of Nevirapine) showing atrophy of the pyramidal cells, and reduction in number of neuronal cells when compared with the control group A H/E X 400

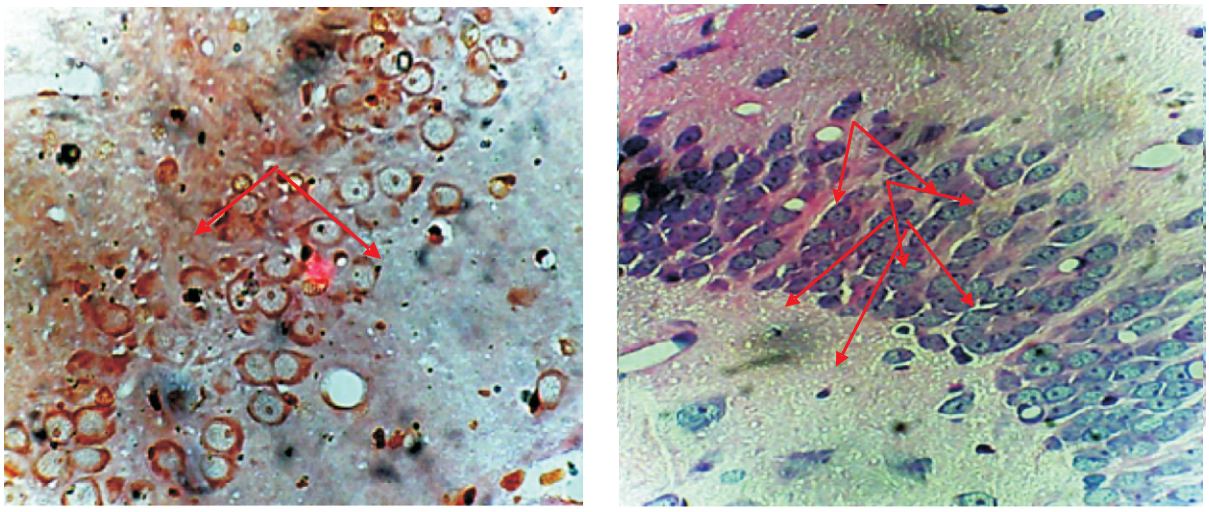

Plate IIa and Iib Photomicrograph of the histology of the Hippocampus of group B treated with 2.86mg/kg of Nevirapine showed atrophy of pyramidal cells and smaller neuronal cells, when compared with the control group A

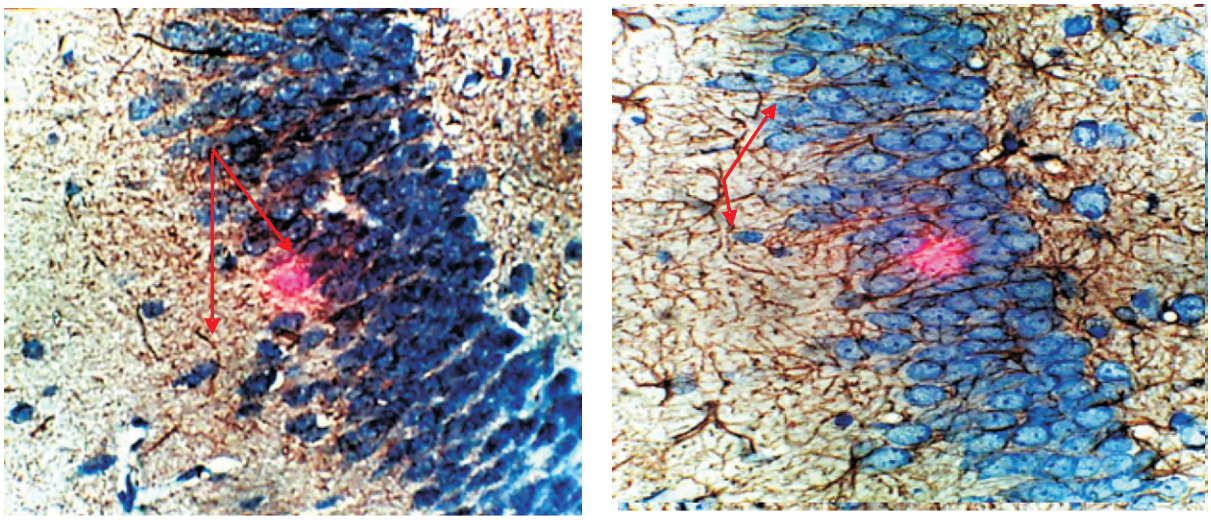

Plate IIIa and IIIb: Photomicrograph of the histology of the Hippocampus of control A and group B treated with 2.86mg/kg of Nevirapine showing increased expression of GFAP by astrocytes (arrow) and in group B treated with Nevirapine than the control group GFAP X 400

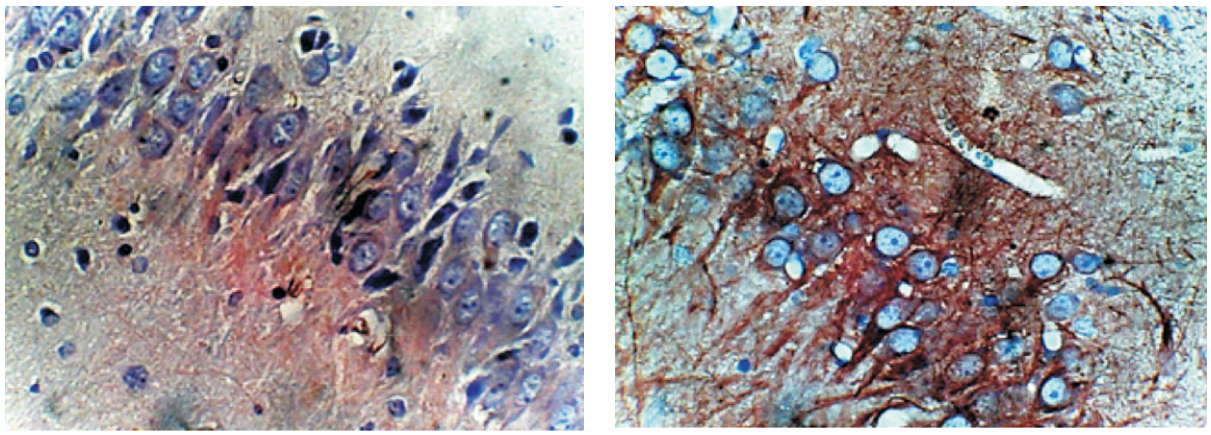

Plate IV a and IV b Photomicrograph of the histology of the Hippocampus of group B treated with 2.86mg/kg of Nevirapine showed increased expression of NF (arrows) and more cellular population stained in group B treated with Nevirapine than the control group NF X 400

DISCUSSION

In this study the group treated with nevirapine showed distortions in the three hippocampal layers; polymorphic, pyramidal and molecular layers with shrinkage of the pyramidal cells and atrophy of the neuronal cells as seen in the Haematoxylin/Eosin and Silver impregnation method. It has been reported that nevirapine impairs recognition memory in mice[10]. Also antiretroviral drugs have been reported to cause dementia in patients[11]. The hippocampus and its connections are necessary for the consolidation of new or short term memories[12]. Damage to the hippocampus may lead to memory impairment, but little is known concerning the extent of hippocampal atrophy in HIV patients due to the effect of the drugs and how it relates to cognition and memory.

These findings were further supported by immunochemical studies which showed increased expression of GFAP by astrocytes and increased expression of NF by neurons in group B that was administered with nevirapine. A study had reported that it damages the liver, kidney and testis[13]. Glial fibrillary acidic protein is an astrocyte-specific intermediate filament protein whose expression is required for fibrous astrocyte normal function including maintenance of CNS white matter and blood–brain barrier integrity[14,15]. These findings suggest that chronic nevirapine administration can lead to hippocampal damage which may lead to memory impairment, because hippocampus plays a major role in memory consolidation[12].

CONCLUSION

Nevirapine is harmful to the histopathology of the hippocampus of Wistar rats. The drug should be taken with caution with periodic neurologic assessment of patients at risk.

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