

Concentration-Effect, Incidence and Mechanism of Nevirapine Hepatotoxicity

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ABSTRACT

Nevirapine is a dipyridozeponone non nucleoside reverse transcriptase inhibitor 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. Nevirapine is used as one of the components of highly active antiretroviral therapy in HIV patients and in the prevention of mother to child transmission of HIV. Reports have linked nevirapine containing highly active antiretroviral therapy with hepatotoxicity which is of great clinical concern. In this study, a comprehensive literature review on reports (previous and present) of nevirapine associated hepatotoxicity in experimental animal studies and humans (case reports, clinical trials and cohorts' studies) was performed. The relationships between length of nevirapine therapy, plasma concentration and nevirapine associated hepatotoxicity were evaluated. The possible mechanisms of nevirapine associated hepatotoxicity were also reviewed. Analysis of data from various clinical trials, cohort and other studies involving patients taking nevirapine containing antiretroviral therapy showed that nevirapine could be hepatotoxic. Nevirapine associated hepatotoxicity is of two distinguished types the early immune mediated hypersensitivity reaction which develops within 18 weeks and the late onset hepatotoxicity which occurs after 18 weeks of nevirapine therapy. Most nevirapine associated hepatotoxicity manifested as hepatitis, jaundice, cholestatic hepatitis, hepatic necrosis and fulminant hepatic failure with rare deaths. This hepatotoxicity is associated with elevation in levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and other biomarkers of liver function. Liver enlargement and necrosis which occurred in centrilobular and mediolobular region marked with inflammations are features of nevirapine associated hepatotoxicity. Nevirapine hepatotoxicity might have correlation with length of therapy but with discrepancy in reports on the relationship between nevirapine hepatotoxicity and nevirapine plasma concentration. The mechanism of nevirapine associated hepatotoxicity is not well understood but could be attributed to direct toxic effect on the liver, mitochondrial dysfunction in hepatocytes, hypersensitivity reaction and stress induced by nevirapine. It is recommended that liver function should be evaluation for HIV patients eligible for nevirapine containing highly active antiretroviral therapy.

Keywords: Nevirapine, Toxicity, Mechanism, Plasma Concentration, Liver

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus known to be the primary cause of Acquired

Immune Deficiency Syndrome (AIDS). The HIV/AIDS epidemic has cause death in many countries. It is reported that about 39 million people globally are living with HIV. The high HIV/AIDS related morbidity and

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mortality in developed countries has been dramatically reduced by the advent of effective combination of antiretroviral therapy (Emejulu *et al.*, 2010). Antiretroviral therapies hamper the growth of the HIV virus, thereby causing the suppression of viral particle multiplication and eventually leading to decreased viral load, thereby prolonging the patient's life span. The impediments to effective use of Highly Active Antiretroviral Therapy (HAART) include the adverse effects associated with the use of these drugs. One of the adverse effects associated with highly active antiretroviral therapy is hepatotoxicity and is frequently reported in patients taking nevirapine containing highly active antiretroviral therapy. Case reports, clinical trials and other studies have linked nevirapine with hepatotoxicity in HIV patients taking nevirapine containing HAART.

Nevirapine is reported to be associated with early hypersensitivity reactions which can cause fulminant hepatitis leading to hepatic failure and death. It is also associated with late onset hepatotoxicity leading to liver enzymes elevation (Soriano *et al.*, 2008). The World Health Organization (WHO) therefore recommends the use of nevirapine with caution and regular monitoring in patients who have baseline grade 1, 2 or 3 elevations of liver enzymes and HBV or HCV (WHO, 2006). In addition, nevirapine is not recommended in patients with a grade 4 elevation of liver enzymes. In January and March 2005, respectively, the US Food and Drug Administration (USFDA, 2005) and European Medicines Agency (EMA) issued warnings in nevirapine package insert recommending against the initiation of nevirapine in adult women with CD4 count above 250 cells/mls or in men with count above 400 cells/mls, because of a higher risk of hepatotoxicity. These data were derived mainly from a retrospective analysis of the Boehringer Ingelheim databases and further confirmed in a sub-analysis of the 2NN study (Stern *et al.*, 2003; Vanleth *et al.*, 2005). This research is in two parts. In this first part we reviewed reported (previous and present) cases of nevirapine hepatotoxicity in animals and humans. We further analyzed reports on the relationship between the length of therapy, nevirapine plasma concentration and hepatotoxicity. The possible mechanisms of nevirapine induce hepatotoxicity were also evaluated. The second part which is on course is on the risk factors associated with hepatotoxicity caused by nevirapine containing HAART.

1.1. Pharmacology of Nevirapine

Nevirapine was the first dipyridozeponone 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 (Harris and Montainer, 2000). It is easy to administer and is generally well absorbed. The pharmacokinetics of nevirapine is characterized by rapid and nearly complete oral absorption, rapid distribution and prolonged elimination (Cheeseman *et al.*, 1993). 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. Nevirapine has a volume of distribution of $1.21 \pm 0.09 \text{ L kg}^{-1}$ (Smith *et al.*, 2001; Podzamcer and Fumero, 2001). 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 (Mirochnick *et al.*, 1998). 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 (Murphy and Montaner, 1996). Resistance leading to clinical treatment failure can occur with mutation at codon 100, 103, 106 and 108 of reverse transcriptase enzyme (Kuritkes, 2004; Eshleman *et al.*, 2009). In vitro studies using human liver microsomes, demonstrated that CYP3A4 and CYP2B6 are primarily responsible for the oxidative metabolism of nevirapine to its major metabolites, although other CYP enzymes may have a secondary role (Erickson *et al.*, 1999; Smith *et al.*, 2001). Nevirapine metabolism is subject to auto induction of CYPs including CYP3A4. This results in decrease in the terminal half-life from 45 h following a single dose to approximately 25-30 h after multiple dosing. The urinary excretion of nevirapine is minor, since only a small fraction (<3%) is eliminated as parent compound in urine (Murphy and Montaner, 1996).

Nevirapine has been linked to some potentially serious adverse effects. One of these effects is nevirapine rash which is characterized by macular or papular 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 (Johnson and Barabouitis, 2000). Severe and fatal hepatotoxicity has been reported with nevirapine use

(Harris and Montaner, 2000; Dieterich *et al.*, 2004). 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.

1.2. Classification of Hepatotoxicity

Liver toxicity is defined as an increase in aspartate Aminotransferase (AST) or alanine Aminotransferase (ALT) levels 5 times above the upper limit of normal (corresponding to WHO grade 3-4 toxicity). There have been discrepancy in the classification of hepatotoxicity. A standard toxicity grade scale is available and is used by AIDS research group. Patients with normal AST and ALT levels before treatment are classified with respect to changes relative to the upper limit of normal UNL. Hepatotoxicity is classified as grade 0 (<1.25× ULN); grade 1(1.25-2.5× ULN); grade 2 (2.6- 5× ULN); grade 3 (5.1-10× ULN) and grade 4 (>5×ULN). Severe hepatotoxicity is defined as grade 3 and grade 4 changes in AST and/or ALT levels during highly active antiretroviral therapy (Kontorinis and Dieterich, 2003).

1.3. Nevirapine Associated Hepatotoxicity

Nevirapine associated hepatotoxicity has been a front burner especially in HIV patients taking nevirapine containing antiretroviral regimens. Reports have shown that there are two distinct types of nevirapine associated hepatotoxicity with characteristic features. The first type of nevirapine associated hepatotoxicity is an immune mediated hypersensitivity reaction which develops within 18 weeks of nevirapine therapy and it is said to be an early onset hepatotoxicity (AIDS INFO). The second type of nevirapine mediated hepatotoxicity occurs after 18 weeks of nevirapine therapy and it is said to be late onset and dose related (Mratinez *et al.*, 2001; Clarke *et al.*, 2000; Sulkowski *et al.*, 2002). Furthermore, nevirapine hepatotoxicity is said to be associated with some risk factors which include, gender, CD4 cell count, co-infection with hepatitis B or C and pregnancy which will be reviewed in the second part of this work (Timmermans *et al.*, 2005; Taiwo, 2006; Torti *et al.*, 2007; Jamisse *et al.*, 2007). In this review we were able to collect and analyze available information on case reports, clinical trials and other studies on nevirapine associated hepatotoxicity. Reported hepatotoxic effect of nevirapine in experimental animals

was also captured in this work. The correlation between nevirapine plasma concentration and hepatotoxicity is discussed in the light of reported literature.

1.4. Nevirapine Hepatotoxicity in Animals

Animal models are used for experimental screening of pharmacological agents. Some pharmacological effects produced by drugs in experimental animals could reflect same or similar pharmacological effects in humans. This is Probably due to some similarities between humans and some animals. There are reports of nevirapine associated hepatotoxicity in experimental animal studies. In this aspect of our work we reviewed available information on nevirapine associated hepatotoxicity in experimental animals.

We will open this discussion with the work of Adaramoye *et al.* (2012) who investigated the toxic effects of 18 and 36 mg kg⁻¹ of nevirapine in rats. Among other findings nevirapine was observed to increase the relative weight of the liver and elevated liver enzymes. Histopathological findings showed that nevirapine caused severe necrosis in the liver of the rats. Adewale *et al.* (2012) also evaluated the effects of co-administered lamivudine, nevirapine and zidovudine on hematological parameters and liver histology in female wistar rats. One of the outstanding findings is the hepatotoxic effect of this combination. This hepatotoxic effect was attributed to the presence of nevirapine in the administered regimen.

The adverse hepatic effect associated with the administration of nevirapine, lamivudine and stavudine was further studied using albino rats by Umar *et al.* (2008). In association with other findings they showed that both acute and sub-chronic administration of nevirapine resulted in significant increase in activities of aspartate aminotransferase and alanine amino transferase. They concluded that nevirapine could be associated with hepatotoxicity (Umar *et al.*, 2008).

In a comparative toxicological evaluation of the hepatotoxic effects of some antiretroviral drugs on wistar albino rats, 200, 30 and 150 mg of nevirapine, stavudine and lamivudine were administered respectively. Comparatively nevirapine produced the highest abnormality in the liver function of treated rats via abnormal elevation of liver enzymes (Sule *et al.*, 2012). Comparatively some researchers have shown lack of disparity between nevirapine associated hepatotoxicity and other antiretrovirals (Bruck *et al.*, 2008). In continuation of the evaluation of the hepatotoxic effect of nevirapine Kayode *et al.* (2011) evaluated the

hematological and hepatic enzyme alterations associated with acute administration of some antiretroviral drugs. They showed that short term administration of SNP40 a drug containing stavudine, lamivudine and nevirapine to rats couldn't produce any significant change in the levels of aspartate aminotransferase and alanine aminotransferase when compared with the control. In the light of available literature, the hepatotoxic effect of nevirapine in animals is associated with elevation of liver enzymes with few incidences of liver necrosis.

1.5. Hepatotoxicity of Nevirapine in Humans

The use of nevirapine containing highly active antiretroviral therapy has tremendously reduced the progression of HIV disease. However hepatotoxicity is one of the limiting factors militating against the use of nevirapine containing highly active antiretroviral therapy in humans as reported in some clinical trials, cohort studies and case reports. In this part of the review we critically analyzed some of the reported studies carried out.

1.6. Clinical and Cohort Studies

We were able to collect reports from different quarters on nevirapine containing antiretroviral therapy associated with hepatotoxicity. One of these reports is the work of the Adult Aids Clinical Trial Group. They analyzed 21 studies involving 10611 patients and found that severe hepatotoxicity was observed in patients administered nevirapine containing antiretroviral drug and discontinuation of nevirapine was reported. Reister and colleagues further found that the rate of hepatotoxicity was 8.9% (95% Confidence Interval (CI) 6.6 to 11.2%) and 10.8% (95, CI 3.3 to 18.3%), respectively, among patients receiving nevirapine and efavirenz. These two drugs were significantly more likely to be associated with grade 3 or 4 elevation of transaminases (Prakash *et al.*, 2001). In a study involving 568 patients receiving NNRTI containing antiretroviral regimens, 312 and 256 patients received efavirenz and nevirapine respectively. Severe hepatotoxicity occurred throughout the duration of NNRTI therapy and was very common among patients taking nevirapine and co-infected with HBV (Sulkowski *et al.*, 2002). This was further supported by the evaluation of Four hundred and sixty eight (468) subjects which were enrolled in a study between August 1999 and February 2000. Two hundred and thirty four (234) subjects were randomized to receive lamivudine. Eighty-two percent of subjects (385/468) were enrolled in the nevirapine group. The frequency of

hepatotoxicity was 17% (66/385) in the nevirapine group and 0% (0/83) in the efavirenz group.

To investigate the incidence of hepatotoxicity in Acquired Immune Deficiency Syndrome (AIDS) patients taking nevirapine containing HAART, 330 AIDS patients were enrolled in this retrospective study. Two hundred and sixty seven (267) out of 330 patients received nevirapine based highly active antiretroviral therapy while 63 cases received efavirenz based highly active antiretroviral therapy. It was observed that 133 out of 267 (49.8%) patients on nevirapine based highly active antiretroviral therapy had at least one episode of alanine aminotransferase elevation. Conclusively it was reported that nevirapine related hepatotoxicity was common among naive HIV infected patients in this cohort study (Gao *et al.*, 2010).

Furthermore Chu *et al.* (2010) conducted a study involving 1809 HIV-infected naive adults initiating nevirapine-based antiretroviral therapy. The primary outcome of this study was early hepatotoxicity while the secondary outcome was hepatotoxicity and mortality at six months. In a study involving 930 HIV-infected patients who were placed on nevirapine between 1998 and 2003, it was reported that the rate of severe hepatotoxicity due to nevirapine was high (Jonckheere *et al.*, 2012). This was supported by a comprehensive analysis of 17 randomized clinical trials of nevirapine treated patients; results showed that 10% of all nevirapine treated patients had elevated levels of alanine aminotransferase and aspartate aminotransferase enzymes greater than 5 times the ULN. Almost two-third (6.3%) of nevirapine treated patients with elevated alanine aminotransferase or aspartate aminotransferase enzymes were asymptomatic. Symptomatic hepatic events were seen in 4.9% (3.2-8.9%) of nevirapine treated patients (Dieterich *et al.*, 2004).

Martinez *et al.* (2001), in a prospective cohort study evaluated 610 patients who were prescribed nevirapine-containing antiretroviral regimens. They reported that hepatotoxicity was common in HVI-1-infected patients receiving nevirapine-containing regimens and the incidence steadily increased overtime.

A study of 540 HIV adult patients who were monitored consecutively taking (d4T/3TC/NVP) Fixed-Dose Combinations (FDC) was performed by Meyssonier and colleagues. Pregnant woman, hepatitis B and C patients were excluded. Among 497 patients with at least two alanine aminotransferase tests, 78 episodes of hepatotoxicity (15.7%) including six cases of grade 3 hepatotoxicity (1.2%) and grade 4 hepatotoxicity or symptomatic hepatotoxicity were reported (Meyssonier *et al.*, 2008).

Five hundred and eighty two (582) patients receiving nevirapine as a component of highly active antiretroviral therapy containing (72% males) were used in this study. Among other parameters evaluated, 10.2% of treated patients manifested a grade 3 or greater increase in aminotransferase levels reflecting an overall incidence rate equal to 5.3 cases/100 person/years. This led to treatment discontinuation in 3.9% of the cases. Conclusively they reported that the risk of nevirapine containing antiretroviral regimens associated hepatotoxicity was low. They advised that it should be used with caution in patients with hepatitis and elevated liver enzymes (Magiolo *et al.*, 2007). In the light of the above reports, there is evidence to show that nevirapine could be associated with hepatotoxicity. The rate of mortality with respect to nevirapine associated hepatotoxicity was quite low only limited cases were observed. The rate of discontinuation of nevirapine due to nevirapine associated hepatotoxicity was also reported and this may not hinder the clinical use of nevirapine except when risk outweighs benefit.

1.7. Case Report

Off recent there are increasing case reports on hepatotoxicity associated with nevirapine during therapy in humans. We systematically collected and analyzed some of these reports. One of these case reports was documented by Buyse *et al.* (2006). He and co researchers reported a case of liver transplant due to nevirapine associated fulminant hepatitis; laboratory evaluation revealed elevated levels of alanine amino transferase, aspartate amino transferase, gamma glutamyl transpeptidase and total bilirubin. Liver biopsy showed massive necrosis in the centrilobular and mediolobular areas, coagulative necrosis was associated with inflammatory reaction. Bera *et al.* (2012) also reported two cases of maternal death following therapy with nevirapine containing antiretroviral regimen. In these patients, liver function was observed to be abnormal due to elevation in liver function parameters. Hepatotoxicity associated with nevirapine was also reported by Baichi (2003). He reported a case of nevirapine induced hepatitis in a 48yr old male. This was characterized by hepatomegaly and abnormal liver function which was associated with abnormal elevation of liver enzymes. Similar observation was also reported (Reiter, 1997; Bundow *et al.*, 2001).

The above case report was supported by the work of Pillero and Bonnie who documented a case of hepatotoxicity suspected to be induced by nevirapine.

Laboratory evaluation showed abnormal elevation in liver enzymes; similar observations were reported by some scholars (Mens and Katzenstein, 2005). Nevirapine has also been shown to be associated with hepatic failure as observed by Cattelan *et al.* (1999). This case report was associated with jaundice and hepatomegaly; laboratory evaluations disclosed abnormal elevation of liver enzymes. Ultrasonography disclosed enlargement of the liver with a non homogenous echo texture and abundant ascites.

Furthermore, therapy with nevirapine containing antiretroviral regimen was reported to be associated with immunoallergic hepatitis. Like most case reports it was also associated with abnormal elevations of liver enzymes and jaundice (Knudtson *et al.*, 2003). Gokengin and Yamazahan (2002) reported two cases of life threatening hepatotoxicity in health workers who were administered nevirapine for post exposure prophylaxis. One of the cases required liver transplant after developing fulminant hepatitis and end stage hepatic failure (Johnson and Baraboutis, 2000). From March 1997-September 2000 FDA received 22 cases of serious adverse events related to nevirapine taken for post exposure prophylaxis. These 22 events include 12 cases of hepatotoxicity (CDC, 2001).

Patel *et al.* (2004) described 30 cases of hepatotoxicity including 14 severe cases and one case of fulminant hepatic necrosis associated with nevirapine post exposure prophylaxis; although they concluded that the presence of other antiretrovirals must have augmented the effect of nevirapine associated hepatotoxicity. Manfred (2001), also reported two cases of health care workers with possible exposure to human immunodeficiency virus who developed adverse reactions after receiving multiple doses of nevirapine/zidovudine/lamivudine as Post Exposure Prophylaxis (PEP). One of the patients developed fulminant hepatic failure resulting to liver transplant.

Maniar *et al.* (2006) published a case of fulminant hepatitis associated with nevirapine containing regimens zidovudine/lamivudine/nevirapine (AZT/3TC/NVP). Abdominal ultrasound revealed hepatomegaly, fatty infiltration, gall bladder wall thickening, bulky pancreas and moderate ascites. A case of severe leucopenia associated with mild hepatotoxicity in a HIV carrier treated with nevirapine was reported by Shahar *et al.* (2004). This was characterized by abnormal elevation of liver enzymes. Initially this patient was placed on zidovudine/lamivudine/indinavir. Because of mild symptoms of hypo dystrophy the indinavir was replaced with nevirapine.

1.8. Nevirapine Concentration and Hepatotoxicity

The pharmacology of nevirapine makes it an attractive candidate for therapeutic drug monitoring, as previous studies have indicated a significant relationship between nevirapine trough concentrations and virologic response (Veldkamp *et al.*, 2001; Vries-Sluijs *et al.*, 2003). Also, high concentrations were linked to increase risk of liver toxicity and hepatic injury in patients with chronic hepatitis C (Dailly *et al.*, 2004; Nunez *et al.*, 2003; Kappelhoff *et al.*, 2005). Inter-individual variability of nevirapine plasma concentrations among HIV infected adults was common in routine clinical practice (50%). The variability could be partially explained by the differences in ethnicity, gender, polymorphisms in enzyme, transporter genes, hepatitis and concomitant medications (Haas, 2005; Kappelhoff *et al.*, 2005; Ma *et al.*, 2005; Stohr *et al.*, 2008).

Requena *et al.* (2002) investigated the effect of nevirapine plasma concentration on liver enzyme elevations and observed that among patients with chronic hepatitis C coinfection, nevirapine concentrations $>6 \text{ mg mL}^{-1}$ were associated with 92% risk of liver toxicity. Therefore, monitoring nevirapine levels, especially in individuals with chronic hepatitis C co infection, might be warranted. However, a prospective population pharmacokinetic study and the 2NN study suggested no correlation between nevirapine trough concentrations and liver enzyme levels (Dailly *et al.*, 2004; Kappelhoff *et al.*, 2005).

Furthermore, in a research to establish a relationship between nevirapine plasma concentration and hepatotoxicity, 227 HIV-infected patients taking nevirapine were evaluated. Their Blood samples were taken 12hr post dose and 24 h post dose for measurement of nevirapine concentration six months after treatment initiation. Result showed that nevirapine hepatotoxicity was associated with median nevirapine trough concentration among male patients and hepatitis C virus co-infection. Among the 227 patients screened 191 patients were qualified for the liver toxicity analysis. The incident of liver toxicity was 71% (136/191) including 43 patients (23%) with severe liver toxicity within 12 weeks of starting therapy. The correlation between nevirapine concentration, efficiency and hepatotoxicity suggested the benefit of dosage adjustment based on therapeutic drug monitoring (Wang *et al.*, 2011). A study to assess the differences in the pharmacokinetics of nevirapine between patients with HIV/HCV coinfection and HIV infection that could explain higher rates of

hepatotoxicity was performed. In this study 18 patients; with seven (7) HIV/HCV coinfection and eleven (11) HIV non- infected were used. Observation in this study highlights the possibility of accumulating drug levels under nevirapine therapy and thus pharmacokinetics measurement in individual cases with expected nevirapine-associated hepatotoxicity may be warranted (Vogel *et al.*, 2009). This agreed with an evaluation of toxicity data for 8216 patients treated with nevirapine containing antiretroviral regimens which showed that duration of nevirapine therapy may influence the outcome of nevirapine associated hepatotoxicity. Results also showed that increased duration of nevirapine therapy could predict nevirapine hepatotoxicity (McKoy *et al.*, 2009).

Maat *et al.* (2002; 2003) evaluated 174 individuals infected with HIV and observed that the plasma concentration of nevirapine does not appear to be a risk factor in nevirapine associated hepatotoxicity. A prospective pharmacokinetic study of nevirapine was performed to test the relationship between hepatotoxicity and nevirapine trough plasma concentration and to identify which covariate could influence nevirapine pharmacokinetics. In this prospective study seventy-seven (77) HIV infected patients were used. It was observed that nevirapine trough plasma concentration has no correlation with hepatotoxicity (Dailly *et al.*, 2004). This is in resonance with an investigation of the relationship between total and unbound plasma concentration of nevirapine and liver enzymes (Alanine amino transferase and Gamma-glutamyl transferase). A total of eighty-five (85) HIV infected patients taking nevirapine containing antiretroviral were used; result showed that there was no strong association between nevirapine concentration and hepatotoxicity (Almond *et al.*, 2004)

Dong *et al.* (2012) evaluated the relationship between nevirapine pharmacokinetics and rash/hepatotoxicity in three hundred and fifty nine (359) women starting antiretrovirals. Among other observations it was reported that hepatotoxicity is not associated with higher nevirapine exposure. There are opposing views with respect to the information collected on the effect of nevirapine plasma concentration and nevirapine associated hepatotoxicity. This leaves more room for further evaluation.

1.9. Mechanisms of Nevirapine Hepatotoxicity

The mechanism of nevirapine induced hepatotoxicity is not well understood but it is known that drug induce

hepatotoxicity can occur through different mechanisms (Lee, 2003). Some of the possible mechanisms of drug induce hepatotoxicity include direct toxicity, mitochondria damage and hypersensitivity reaction (Grattagliano *et al.*, 2002; Dykens and Will, 2007).

1.10. Direct Toxicity

Nevirapine and some drugs are known to be metabolized by the liver hence could induce direct toxicity on the liver. Drugs metabolized by the liver through the Cytochrome pathway may cause liver toxicity when there are polymorphisms in the enzymes (Bissell *et al.*, 2001). The most important drug metabolizing enzyme for the creation of hepatotoxic reactive metabolites is the polymorphic Cytochrome P450 (CYP450) family that mediates oxidative phase-I drug metabolism. However, conjugative phase-II metabolism may also result in hepatotoxic metabolites, e.g., acyl glucuronides are well known to cause DILI (Spahn-Langguth and Benet, 1992; Boelsterli, 2002). Reactive metabolites can exert initial cell stress through a wide range of mechanisms including depletion of glutathione (GSH), or binding to enzymes, lipids, nucleic acids and other cell structures. Furthermore reactive metabolites or parent drugs may specifically inhibit other hepatocellular functions (Pauli-Magnus *et al.*, 2005). Since many of the antiretroviral drugs are metabolized by liver enzymes polymorphism in the enzymatic complexes might lead to heterogeneity in drug metabolism. This can lead to the development of hepatotoxicity in some individuals. Some drugs might stimulate or activate stress pathway leading to hepatic stress which could be observed in nevirapine (Leist *et al.*, 1998).

1.11. Hypersensitivity Reaction

Hypersensitivity reaction is an idiosyncratic reaction exhibited by the host with respect to an administered drug. Allergic idiosyncratic hepatotoxicity is characterized by the presence of typical symptoms and signs of adaptive immune reactions, including fever, skin reactions, eosinophilia, formation of autoantibodies and a short latency time particularly after re-exposure (Rusmann *et al.*, 2009). Hypersensitivity could be immune mediated. Mediated immune drug reaction could be associated with the generation of neoantigens produced by the reaction of liver proteins with reactive drug metabolites. Several authors have linked nevirapine with hypersensitivity reactions (Martin *et al.*, 2005; Pilliero and Purdy, 2001). Nevirapine hypersensitivity is

said to develop in the first few weeks of therapy and is characterized by rash, fever, hypotension along with hepatic dysfunction (Johnson and Baraboutis 2000).

1.12. Mitochondria Toxicity

Drugs (or their metabolites) can induce mitochondrial dysfunction in hepatocytes through several mechanisms. One of these mechanisms is the induction of MPT. Several drugs can trigger MPT in liver mitochondria, leading to apoptosis and/or necrosis. These drugs cause 'cytolytic' hepatitis, leading occasionally to fulminant hepatic failure. Some drugs (or metabolites) can directly trigger MPT in isolated mitochondria (Pessayre *et al.*, 2007; Trost and Lemasters, 1996; Masubuchi *et al.*, 2006). The molecular mechanisms whereby these drugs induce MPT are often poorly understood. FAO impairment can also lead to mitochondrial dysfunction in hepatocytes. Drugs can also impair the mitochondrial oxidation of fatty acids, leading to their accretion as triglycerides in the cytoplasm of the hepatocytes. Although free fatty acids can also accumulate, this seems to happen preferentially when FAO is severely inhibited (Fromenty and Pessayre, 1995). FAO can be impaired in different ways. Some drugs directly impair mitochondrial FAO by inhibiting FAO enzymes (Deschamps *et al.*, 1991; Pessayre *et al.*, 1999; 2007).

Furthermore NRTIs are known to induce mitochondria damage. Human mitochondrial DNA polymerase is inhibited by NRTIs (Kontorinis and Dieterich, 2003). Depletion of mitochondrial DNA impairs the cellular respiration chain and inhibits pyruvate and folic acid pathways. Mitochondrion appears enlarged and swollen with metrical densities and occasional vacuoles (Moyle, 2000). In severe NRTIs mitochondria toxicity, macrovascular hepatic cholestasis, giant mitochondrial and intrahepatic cholestatic will be observed (Moyle, 2000; Spengler *et al.*, 2002).

2. CONCLUSION

In this review it is discovered that nevirapine might be hepatotoxic. Liver function status of HIV patients eligible for nevirapine should be evaluated. Especially in patients with HIV/Hepatitis coinfection. Also coadministration of nevirapine with other drugs that have adverse hepatotoxic effect or could potentiate the hepatotoxic effect of nevirapine should be avoided or use with caution.

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