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Case Report

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Hepatic adverse events during highly active antiretroviral therapy containing nevirapine: a case report

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Abstract

Background: Hepatotoxicity is one of the most serious complications of highly active antiretroviral therapy (HAART). The aim of this report is to analyse an HIV infected patient on HAART including nevirapine and taking antidepressive agents, with acute toxic hepatitis.

Case presentation: A 39 year old patient diagnosed as HIV positive one month ago administered to the clinical ward of the Department of Infectious Diseases and Clinical Microbiology in Ege University Medical School with high fever, malaise, nausea, diarrheae and elevated liver enzymes (ALT 1558 U/L, AST 4288 U/L). He has been using HAART including zidovudine+lamivudine (2 × 1/day) and nevirapine (2 × 200 mg/day, following dose escalation) for 22 days, sertralin and diazepam for 12 days and lithium for 10 days.

The patient was hospitalized. Antiretroviral and antidepressant treatments were stopped. The day after admission, his fever dropped and his symptoms improved. Clinical improvement continued on the following days. The patient was discharged upon his request on the 14th day of hospitalization. The liver function tests returned to normal levels in two weeks following discharge.

Conclusion: Close monitoring of liver enzymes during the first 12 weeks of nevirapine therapy is critical to prevent life threatening events.

Background

Hepatotoxicity is one of the most serious complications of highly active antiretroviral therapy (HAART). While hepatotoxicity was described for all antiretroviral classes, ritonavir was attributed the highest risk among all drugs [1,2].

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) frequently used in HAART regimens. The most common adverse event encountered during NVP use is cutaneous rash. Recently severe hepatic reactions attributed to NVP administered as part of HAART or in post-exposure prophylaxis (PEP) regimens, have also been reported [3–6].

In this report, we present an HIV infected patient on HAART including nevirapine and taking antidepressive agents, with acute toxic hepatitis.

Case presentation

A 39 year old HIV positive patient on HAART followed up by the authors, administered to the clinical ward of the Department of Infectious Diseases and Clinical Microbiology in Ege University Medical School with high fever,

malaise, nausea and severe diarrheae. He had administered to the State Hospital the day before and was transferred to our hospital upon the detection of highly elevated liver enzymes (ALT 1558 U/L, AST 4288 U/L).

The patient was diagnosed as HIV positive one month ago and has been using HAART including zidovudine+lamivudine (2 × 1/day) and nevirapine (2 × 200 mg/day, following dose escalation) for 22 days. He was also under psychiatric control due to severe depression and has been using sertralin and diazepam for 12 days and lithium for 10 days. His baseline plasma viral RNA was >75.000 copies/mL, baseline CD_4+ T cell count 277/mm^3, and liver function tests were normal. He had been asked to refer to the hospital weekly during the first month of HAART for routine tests; but he did not return to the hospital for these routine controls.

Physical findings revealed low-grade fever (37.6°C), pharyngial hyperemia and seborrhoeik dermatitis on both cheeks. Routine laboratory test results on admission were as follows: hemoglobin 13.8 g/dL; white blood cell count 4.3 × 10^3/mm^3 with 58.6% neutrophiles, 22.5% lymphocytes, 6.5% monocytes, and 12.4% eosinophils; platelets 2.4 × 10^7/mm^3, erythrocyte sedimentation rate 42 mm/hr, blood urea nitrogen 83 mg/dL, serum creatinine 2.36 mg/dL, AST 2221 U/L, ALT 377 U/L, ALP 577 U/L, GGT 246 U/L, total bilirubine 1.70 mg/dL, direct bilirubine 1.57 mg/dL.

The patient was hospitalized. Antiretroviral and antidepressant treatments were stopped. Since the oral intake of the patient was low, infusion of balanced electrolyte solutions were started. Blood, pharyngial, stool and urine cultures were performed and all were negative for any pathogens. *Cryptosporidium* and *Blastocystis hominis* cysts were identified in the examination of direct and stained stool specimens. The patient was immune to hepatitis A, vaccinated and anti-HBs positive for hepatitis B, and had no serological markers for hepatitis C. IgG antibodies were positive for CMV and EBV viral capsid antigen. His anti-toxoplasma IgM and IgG antibodies were negative. Abdominal ultrasonographic findings and the radiologic examination of the lungs were normal. His viral load has decreased to 525 copies/mL at the end of 22 days of antiretroviral treatment.

The day after admission, his fever dropped and his symptoms improved. Azithromycin 1 g/day was administered for cryptosporidiasis on the second day of hospitalization. Clinical improvement continued on the following days. No rise in fever was observed until the day of discharge. Diarrhea stopped on the sixth day of hospitalization. Liver function tests were controlled every two days. Lower levels were obtained in each test. No other medication was started while he was hospitalized.

The patient was discharged upon his request on the 14th day of hospitalization. His liver function test results on the 14th day were as follows: AST 61 U/L, ALT 156 U/L, ALP 379 U/L, GGT 138 U/L, total bilirubine 1.1 mg/dL, and direct bilirubine 0.75 mg/dL.

He was called for control visits every week. The liver function tests returned to normal levels in two weeks. Azithromycin treatment was stopped at the end of one month. Antiretroviral treatment could not be restarted immediately after total recovery due to the financial problems of the patient. Zidovudine+lamivudine (2 × 1/day) and indinavir (3 × 800 mg) were administered three months after the discontinuation of HAART. Antidepressant treatment was restarted with paroxetine one month after discharge. Following four weeks of antiretroviral treatment, all routine tests of the patient were normal, plasma viral RNA 1950 copies/mL and CD_4+ T cell count 579/mm^3.

Hepatotoxicity is a major side effect of antiretroviral drugs, limiting their use in treatment regimens and in combination with other hepatotoxic drugs. Up to date, hepatic toxicity has been described for all antiretroviral groups [1,2,7]. While the risk of severe hepatotoxicity was indicated to be 5-fold higher for patients taking ritonavir in one study [2], high rate of hepatotoxicity irrespective of drug class was reported in another [1]. Among the NNRTI's NVP or efavirenz (EFV) were significantly more likely to be associated with Grade 3/4 hepatotoxicity [1]. Although NVP toxicity seems to be related to several factors such as the baseline CD_4+ T cell count, baseline ALT and AST levels and coinfection with hepatitis B or C, patients lacking these risk factors may also be prone to the hepatic side effects of the drug [2,6,8,9].

Although not very frequent, antidepressive agents have also been accused of having hepatotoxic side effects [10,11]. Most of these reactions are indicated to be unpredictable and dose-independent [10]. While there are reports on some neuroleptic and psychotropic drugs that should not be used with various antiretrovirals, there is no warning limiting the use of NVP with antidepressants [12]. The fact that the patient presented above has been using three antidepressant drugs together with antiretrovirals complicates the situation. Although studies have clearly demonstrated a hepatotoxic potential for the above stated compounds, it is hard to differentiate which drug is responsible for the adverse event in this case. A possible explanation would be that the combined hepatotoxic effect of antidepressants with NVP have precipitated the hepatic event. The finding that none of the factors considered to be related to the hepatotoxicity of NVP were

present in the patient was also an interesting point to be considered.

Most reports on the hepatotoxicity of NVP indicate that clinical hepatitis is not common and the abnormality in liver function tests are reversible after the discontinuation of the drug [3,5,9]. However, there are other reports describing icteric hepatitis cases which are also reversible, due to NVP [8] and although rare, reports on cases who developed fulminant hepatitis with consequent liver failure either requiring transplantation or being fatal [4]. Due to the high rate of discontinuation, mortality of hepatotoxic events due to NVP is low [1]. As indicated above, the patient presented also recovered totally after the discontinuation of antidepressant and antiretroviral treatment.

Since the antidepressant treatment of the patient had to be continued, a new antiretroviral regimen which did not include NVP was administered to the patient after recovery. Besides, the former antidepressants were replaced with paroxetine due to its low rate of hepatotoxicity. The patient is still closely monitored. He is clinically well and has no abnormal laboratory findings.

Conclusions

The rapidly increasing number of reports on the hepatotoxicity of NVP has drawn the attention to its use in HAART and PEP. NVP has not been recommended for PEP use and should not be included in the regimen due to its serious adverse effects. However it is a good alternative drug in HAART regimens and its hepatotoxic potential should not limit its use in antiretroviral treatment regimens. Close monitoring of liver enzymes during the first 12 weeks of therapy is critical to prevent life threatening events. Discontinuation of the drug permanently may aid in reducing mortality.

Authors' contributions

DG is primarily responsible for the patient's treatment and follow-up

TY assisted Deniz Gokengin in the follow-up

All authors read and approved the final manuscript.

List of Abbreviations

HAART: Highly active antiretroviral therapy

HIV: Human immunodeficiency virus

AST: Aspartam aminotransferase

ALT: Alanine aminotransferase

ALP: Alkaline phosphatase

GGT: Gamma glutamil-transferase

NVP: Nevirapine

EFV: Efavirenz

NNRTI: Non-nucleoside reverse transcriptase inhibitors

CMV: Cytomegalovirus

EBV: Epstein-Barr virus

RNA: Ribonucleic acid

PEP: Post-exposure prophylaxis

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