INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 11(A); November 2020; Page No.5409-5410
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202011930

Research Article

A RARE CASE OF FATAL LACTIC ACIDOISIS AND HEPATITIS WITH TENOFOVIR AND LAMIVUDINE

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ARTICLE INFO

Article History:
Received 06th August, 2020
Received in revised form 14th September, 2020
Accepted 23rd October, 2020
Published online 28th November, 2020

Key words:
HIV, mitochondrial toxicity, lactic acidosis

ABSTRACT

Nucleotide analogues have the potential to cause mitochondrial (mt) toxicity which may lead to the development of lactic acidosis (LA). Tenofovir, a nucleotide analogue-induced LA is extremely rare because of its low affinity for mt DNA polymerase. We report a rare case of tenofovir and lamivudine causing severe hepatitis and lactic acidosis, resulting in death in a seropositive patient with an identifiable risk factor of very low CD4 count.

INTRODUCTION

Tenofovir based highly active antiretroviral therapy (HAART) is one of the preferred first line therapies in management of HIV -1 infection. There is however paucity of scientific data that reflects the safety and efficacy of Tenofovir based therapy. This nucleotide analogue has potential to cause mitochondrial (mt) toxicity which may lead to development of lactic acidosis[1].It is estimated that 8% - 21% of Nucleotide Reverse Transcriptase inhibitor (NRTI) treated patients have hyperlactatemia, while only 1% - 2% develop severe lactic acidosis because of its low affinity for mitochondrial mt DNA polymerase[2].Tenofovir, a nucleotide analogue induced Lactic Acidosis (LA) is extremely rare. We report a rare case of tenofovir and lamivudine causing severe hepatitis, lactic acidosis and death in a retropositive patient with identifiable risk factor of very low CD4 count

Case Summary

A 31 year old man diagnosed retropositive was started on ART Tenofovir based regimen (Tenofovir lamivudine and efavirenz) and on co trimoxazole prophylaxis with a baseline CD4 count of 1 .Three weeks after administration of tenofovir based regimen patient developed nausea, vomiting, asthenia, muscular weakness and severe abdominal pain. The patient weighed 56.8 kg. The patient was conscious, oriented to time ,place and person , pulse 122/min, blood pressure of 100/60 mmhg in right arm in supine position, respiratory rate 36/min, pallor was noted and dehydration was present. Systemic examination was unremarkable except for diffuse abdominal tenderness.

Hematological investigation revealed a hemoglobin concentration of 9.4 g/dl, a white blood cell count of 3550 cells / mm3 and a platelet count of 150, 000 cells / mm3. mg/dl.His serum sodium concentration was 132 mM, chloride 99 mM , potassium of 5.11 mM , bicarbonate of 11.2 mM.His renal function was normal with serum creatinine of 0.8 mg/dl and urea of 29. mg/dl and serum glucose concentration was 115 mg/dl. Urine routine was normal and negative for ketones. Other laboratory abnormalities included elevated aspartate aminotransferase and alanine aminotransferase 1214.6 U/L and 489.7 U/L respectively, alkaline phosphatase was 787 U/L and gamma Glutamyl transferase of 786 U/L suggestive of cholestatic hepatitis. Serum amylase and lipase was 136 U/l and 272 U/L respectively. HBs ag and anti HCV was negative. Usg abdomen revealed mild fatty infiltration of liver. Arterial blood gas analysis revealed high anion gap metabolic acidosis (PH - 7.288, Pao2 114, PCO2 - 23.9, HCO3- 11.2, lactate-12.88, BE -14.2, anion gap 25.8).

Diagnosis and Intervention

Patient was admitted to medical intensive care unit with provisional diagnosis of Type B lactic acidosis and hepatitis and pancreatitis which were secondary to Nucleotide reverse transcriptase inhibitors (NRTI). Patient was managed with intravenous and oral bicarbonate supplementation, high dose

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thiamine and other supportive measures. Highly Active Antiretroviral Therapy (HAART) was discontinued. But patient eventually succumbed to his illness.

DISCUSSION

We report this case of HIV infected patient on Highly active anti retroviral therapy (HAART) Tenofovir, Lamivudine and Efavirenz who presented with high anion gap metabolic acidosis. Most of the causes of high anion gap acidosis diabetic ketoacidosis, uremic ketoacidosis, alcohol ketoacidosis and drugs like salicylates, isoniazid, metformin, valproic acid were excluded in this patient by clinical history and laboratory examination.

Lactic acidosis is characterised as being one of two types.Type A lactic acidosis is due to hypoperfusion and hypoxia, which occurs when an oxygen consumption and a delivery mismatch occurs, with resulting anaerobic type A lactic Acidosis include all shock states (septic, cardiogenic, hypovolemic, obstructive), regional ischemia (limb .mesenteric) seizures/convulsion, and severe cases of shivering. Type B Lactic Acidosis is defined as not having to do with tissue hypoxia or hypoperfusion. While perhaps less common as compared to type A lactic acidosis, both Type-A and type-B share a fundamental problem of inability of mitochondria to process the amount of pyruvate with which it is presented. Thus alternative metabolic pathways for pyruvate as described in lactic acid cycle become activated which results in excessive levelsof lactate. Examples of type-B lactic acidosis are liver disease, malignancy, medications (metformin, epinephrine), total parenteral nutrition, Nucleotide reverse transcriptase inhibitor therapy, Thiamine deficiency, mitochondrial myopathy, congenital lactic acidosis, trauma, excessive exercise, diabetic ketoacidosis and ethanol intoxication.

Nrti Induced Lactic Acidosis

Severe Type B lactic acidosis is uncommonly associated with highly active anti retroviral therapy (HAART).Although the incidence of mild hyperlactatemia was reported to be as high as 21 % of NRTI – treated patients, the incidence of symptomatic severe hyperlactatemia was lower at 1.3 to 20.9 cases per 1000 treated person years [3]. The clinical features of NRTI induced Lactic Acidosis are non specific with gastrointestinal symptoms being the most common. The patient described here displayed typical symptoms of nausea, vomiting, abdominal pain, asthenia, dyspnoea with elevated transaminases and evidence of fatty infiltration of liver on USG. Other classic findings were low bicarbonate concentration, elevated lactic acid and serum amylase and lipase. The gold standard for diagnosis of NRTI related mitochondrial toxicity, although sometimes impractical in clinical setting, is muscle or liver biopsies which reveal macro or micro vacuolar steatosis. Considering the invasiveness of these procedure and their low anticipated and prognostic value, biopsy was deferred in this patient. The mechanism of NRTI induced lactic acidosis is thought to be secondary to mitochondrial toxicity.

Impaired pyruvate oxidation leads to lactate production and impaired β oxidation results in conversion of fatty acids to triglycerides that accumulate in myocyte and hepatocyte cytosol, causing depletion of kreb cycle substrates and decreased ATP production. There is evidence that NRTI cause Dysfunction of DNA polymerase ϒ an essential enzyme for mitochondrial DNA replication, leading to depletion of mitochondrial DNA. The relative potential of inhibition of mitochondrial DNA polymerase gamma in cell culture have been postulated as Zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir. There are very few case reports of lamivudine causing severe lactic acidosis due to its low potency to cause mitochondrial toxicity[4]. Risk factors of NRTI induced severe lactic acidosis is obesity, female gender, pregnancy, liver Injury and low CD 4 count. In all the reported case patients had underlying risk factor predisposing to mitochondrial toxicity. In the case reported by Murphy *et al*[5], the predisposing factor was preexisting renal insufficiency, co administration of didanosine which has high affinity for mitochondrial DNA polymerase ϒ and use of diuretics. In another case report by Hashim *et al*[6], there was underlying HCV infection, E Coli bacteremia and hypotensive episodes. The present case has an identifiable risk factor of very low CD 4 count.

CONCLUSION

This report emphasizes although tenofovir and lamivudine induced lactic acidosis is rare, its administration should be undertaken with caution. It is imperative for clinicians to be able to recognise the signs and symptoms of lactic acidosis early in NRTI treated HIV patients to institute prompt treatment. Given the high mortality rate between 33 % to 57 %, management needs to be aggressive and include withdrawal of HAART, supportive therapy with intravenous bicarbonate, supplementation of cofactors such as thiamine, riboflavin and carnitine.

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