Iran Red Crescent Med J. 2015 October; 17(10): e19546. DOI: 10.5812/ircmj.19546

Published online 2015 October 24. **Case Report**

Fatal Tenofovir-Associateacd Lactic Acidosis: A Case Report

Hasriza Hashim [1]; Narisa Sulaiman Sahari [2]; Sazlyna Mohd Sazlly Lim [2,*]; Fan Kee Hoo [2]

[1]Department of Medicine, Hospital Putrajaya, Putrajaya, Malaysia
[2]Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

*Corresponding Author: Sazlyna Mohd Sazlly Lim, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia. Tel: +60-389472568, Fax: +60-389472759, E-mail: sazlynalim@gmail.com

Received: April 18, 2014; **Revised:** September 3, 2014; **Accepted:** March 31, 2015

Introduction: The introduction of highly active antiretroviral therapy (HAART), in 1996, has resulted in marked reductions in the rate of illness and death, due to HIV infection. The HAART has transformed HIV infection into a manageable chronic disease. However, although many regimens lower plasma viral load, to below the limit of detection, in most patients, maintaining viral load suppression remains challenging, because of adverse effects and toxicity in the long term, which can lead to non-adherence, virologic failure and drug resistance. Although rare, lactic acidosis often develops fatal complications, as reported in several human immunodeficiency virus infected patients treated with nucleoside reverse transcriptase inhibitors (NRTIs). The purpose of this paper is to report a case of tenofovir induced lactic acidosis and review the literature.

Case Presentation: A 52-year-old Malay gentleman, with hepatitis C virus and HIV infection was admitted to the intensive care unit for severe lactic acidosis, with concurrent *Escherichia coli* bacteremia with multiorgan dysfunction. The patient was started on highly active antiretroviral therapy, which included tenofovir, 5 weeks before presentation. Antimicrobial therapy, continuous veno-venous hemofiltration, and other supportive treatments were instituted. However, the patient eventually succumbed to his illness.

Conclusions: It is essential for clinicians to be able to recognize the signs and symptoms of lactic acidosis in NRTIs treated HIV patients, as an early diagnosis is important to institute treatment.

Keywords: Antiretroviral Therapy; Highly Active; Nucleosides; Transcriptase; Tenofovir; Acidosis; Lactic

1. Introduction

Tenofovir is the first nucleoside reverse transcriptase inhibitor (NRTI) with activity against HIV. It was approved for the treatment of HIV-1 infection in the United States, in 2001, and in Europe, in 2002 (1). Tenofovir inhibits the HIV reverse transcriptase enzyme, which is essential for HIV virus replication. However, highly active antiretroviral therapy (HAART) related adverse drug reactions have been observed, several of which can be life threatening. Lactic acidemia (venous lactate > 2 mmol/L, with normal arterial pH) and lactic acidosis (venous lactate level > 2 mmol/L with arterial pH < 7.3) are potential complications associated with NRTIs (2, 3). In this report, we illustrate the clinical picture of tenofovir associated lactic acidosis.

2. Case Presentation

We report a 52-year-old Malay gentleman, a financial consultant with a background history of hepatitis C virus (HCV) infection, with liver cirrhosis (Child's B), portal hypertension, grade 1 esophageal varices and HIV infection. His baseline HCV RNA load was 374000 IU/mL, CD4 count was 76 cell/uL, CD8 was 588 cell/uL, and HIV viral load was 1210 copies/mL. His HAART regime comprised of oral Tenvir-EM (Tenofovir 300 mg/Emtricitabine 200 mg, Cipla Ltd., Mumbay, India), one tablet daily, and oral efavirenz 600 mg ON. Prior to commencement of HAART, his alanine aminotransferase (ALT) was within normal range (42 mmol/L). He returned for a follow up, one month after he was started on the antiretroviral therapy, and was relatively well. However, one week later, he was brought to the emergency department with a 3-day history of severe epigastric pain, breathlessness, nausea and vomiting. He denied any history of fever, cough, diarrhea, or chest pain.

On physical examination, he was conscious with Glasgow coma scale (GCS) of 14/15. However, he appeared lethargic and dehydrated. His blood pressure was 90/42 mmHg, pulse rate was 133 beats per minute, and temperature was 36° Celsius. He was tachypneic, with respiratory rate of 36 per minute. Oxygen saturation was 92%, under room air. He was mildly icteric. There was no flapping tremor. Auscultation of the lungs revealed minimal crepitations, with reduced vocal resonance, bibasally. His abdomen was soft, with moderate ascites present. There was pitting edema up to the knees, bilaterally. His cardiovascular examination was insignificant.

Laboratory studies revealed severe metabolic acidosis, with arterial blood gas pH of 7.08, HCO3- of 12 mmol/L, base excess of -16.9 mmol/L, and pCO2 of 32 mmHg. His lactate level was 12.4 mmol/L and serum ammonia was 116 mmol/L. Liver enzyme, including ALT was 55mmol/L and bilirubin 37 mmol/L. His infective parameters, including white blood cell count (WBC) (21×10^9) and C-reactive protein (4.0 mmol/L) were elevated. Other blood parameters, including amylase, were unremarkable. The chest radiograph showed minimal interstitial opacities at the bases, bilaterally. Electrocardiogram (ECG) revealed normal sinus rhythm and no ischemic changes.

The patient was intubated and further managed in the intensive care unit (ICU). He was started on intravenous amoxicillin/clavulanic acid 1.2 g twice daily and intravenous metronidazole 500 mg twice daily, to cover for sepsis. Continuous veno-venous hemofiltration (CVVH) was commenced, in view of persistent lactic acidosis, despite of intravenous bicarbonate administration. His antiretroviral therapy was discontinued. Peritoneal fluid analysis and abdominal computed tomography (CT) scan were unremarkable. His repeated CD4 and CD8 cell counts were very low (36 cells/uL and 27 cells/uL, respectively). Blood cultures grew gram-negative rod *Escherichia coli*, which was sensitive to amoxicillin/clavulanic acid. He was treated as septicemic shock, secondary to *E. coli* bacteremia, with multiorgan dysfunction. His lactic acid level remained high, despite daily CVVH, with deterioration in his liver function. Despite CVVH, antimicrobial and supportive treatment, he deteriorated and succumbed to his illness, after 3 days of admission.

3. Discussion

Stavudine and didanosine are two NRTIs frequently associated with lactic acidemia. Tenofovir is less likely to cause hyperlactatemia (4). The NRTI associated lactic acidosis (NALA) is thought to be due to mitochondrial toxicity (5, 6). The NRTIs bind to mitochondrial DNA polymerase-γ, which replicates mitochondrial DNA (mtDNA). The inhibition of mitochondrial polymerase-γ and subsequent inhibition of mitochondrial DNA replication lead to impairment of mitochondrial aerobic metabolism, resulting in accumulation of lactic acid (2, 3). The NALA can develop between 1 to 20 months after the start of HAART (7). Despite their low affinity for mitochondrial DNA polymerase-γ, there are reported cases of tenofovir induced lactic acidosis. Murphy et al. (8) reported a case of fatal lactic acidosis, when tenofovir was added to a patient's antiretroviral regimen, which also included didanosine. Diagnosis of NRTI-related mitochondrial toxicity can be made by muscle or liver biopsy, which will reveal macro and microvacuolar steatosis, although this is rarely practiced, in view of the low anticipated diagnostic value and invasiveness (9).

It is estimated that 8% - 21% of NRTI-treated patients have hyperlactatemia, while only 1% - 2% develop severe lactic acidosis (4). However, the exact incidence is unknown and the reason why only a small number of patients, who receive NRTIs, develop mitochondrial toxicity is still unknown. Identifiable risk factors for the development of lactic acidosis in NRTI-treated HIV patients are pregnancy, female gender, obesity, and liver injury (2). It has been argued that deficiencies in riboflavin and thiamine may predispose patients to the development of lactic acidosis (10). Hepatic dysfunction may play a role in the development of lactate accumulation, since the liver is the most important organ for lactate clearance.

Hyperlactatemia has a wide spectrum of manifestations, which are nonspecific. Patients may present with fatigue or gastrointestinal complaints, such as abdominal pain, nausea, vomiting or diarrhea. Due to the nonspecificity of symptoms, hyperlactatemia may not be recognized for weeks to months. Severe lactic acidosis, on the other hand, may have a more severe presentation, such as hypotension, altered mental status, dyspnea, and cardiac arrhythmias (3). Laboratory parameters usually shows lactate levels of > 5 mmol/L, low arterial pH < 7.3, low serum bicarbonate, increased anion gap, and elevation in liver transaminases. The mortality rate amongst patients with lactic acidosis is very high, between 33% - 57%, mostly due to the resulting liver failure and fatal cardiac arrhythmias (7). Higher lactate levels appear to be linked with higher mortality rates (11).

In our patient, the mechanism of the severe lactic acidosis was multifactorial, which included previous medication with tenofovir, poor tissue perfusion secondary to hypotensive episodes, worsening liver failure and sepsis with *E. coli* bacteremia. Another risk factor for developing lactic acidosis in our patient was his underlying HCV infection.

Serum lactate should be monitored in patients on NTRIs and patients should be advised on the symptoms of lactic acidemia, as it is often nonspecific and may occur at any time. If the serum lactate level is between 2 - 5 mmol/L, then lactate level should be closely monitored. In symptomatic patients, with venous lactate > 5 mmol/L, NRTIs should be discontinued. Management of NRTI-associated lactic acidosis is mainly supportive, consisting of hydration, and intravenous bicarbonate administration and ventilatory support, when needed. After discontinuation of NRTIs, lactic acidemia will generally subside (7).

The NRTIs, such as stavudine and didanosine, are well known to cause severe lactic acidosis, which is often fatal in HIV infected patents. Less commonly, tenofovir has also been demonstrated to have the potential adverse reaction of lactic acidosis. It is essential for clinicians to be able to recognize the signs and symptoms of lactic acidosis in NRTI-treated HIV patients, as the early diagnosis is important to institute treatment, such as prompt initiation of renal replacement therapy. Administration of tenofovir should be undertaken with caution, and patients should be monitored closely for lactic acidosis.

Authors' Contributions

Study concept and design: Hasriza Hashim. Analysis and interpretation of data: Hasliza Hashim, Narisa Sulaiman Sahari and Sazlyna Mohd Sazlly Lim. Drafting of the manuscript: Hasliza Hashim, Narisa Sulaiman Sahari, Sazlyna Mohd Sazlly Lim and Fan Kee Hoo. Critical revision of the manuscript for important intellectual content: Hasliza Hashim, Narisa Sulaiman Sahari, Sazlyna Mohd Sazlly Lim and Fan Kee Hoo.

Funding/Support

This research received no specific grant from the government or any other funding agency in the public, commercial, or not-for-profit sectors.

References

1. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS.* 2007;**21**(10):1273–81.
2. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;**49**(5):651–81.
3. Schambelan M, Benson CA, Carr A, Currier JS, Dube MP, Gerber JG, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr.* 2002;**31**(3):257–75.
4. Boubaker K, Flepp M, Sudre P, Furrer H, Haensel A, Hirschel B, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis.* 2001;**33**(11):1931–7.
5. Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.* 1998;**12**(14):1735–44.
6. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther.* 2000;**22**(6):685–708.
7. Falco V, Rodriguez D, Ribera E, Martinez E, Miro JM, Domingo P, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis.* 2002;**34**(6):838–46.
8. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. *Clin Infect Dis.* 2003;**36**(8):1082–5.
9. Claessens YE, Chiche JD, Mira JP, Cariou A. Bench-to-bedside review: severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors. *Crit Care.* 2003;**7**(3):226–32.
10. Fouty B, Frerman F, Reves R. Riboflavin to treat nucleoside analogue-induced lactic acidosis. *Lancet.* 1998;**352**(9124):291–2.
11. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet.* 1999;**354**(9184):1112–5.