CASE REPORT

Lactic Acidosis in HIV Patients Receiving Highly Active Antiretroviral Therapy

Y W Chow, MRCP, C L Leong, MMed, H L Chow, MBBS, L S Hooi, FRCPE

Department of Medicine, Hospital Sultanah Aminah Johor Bahru

SUMMARY
Exposure to highly active antiretroviral therapy (HAART) may lead to adverse effects related to mitochondrial toxicity such as lactic acidosis. We describe two cases of severe lactic acidosis in HIV-positive patients to illustrate the clinical symptoms and abnormal laboratory results associated with this condition. There is a lack of awareness about the risk factors for developing severe lactic acidosis and recognition of its onset with dire consequences.

KEY WORDS:
HIV, Lactic acidosis, Nucleoside analogue, Highly active antiretroviral therapy, Continuous renal replacement therapy

INTRODUCTION
Highly active antiretroviral therapy (HAART) has become the standard of care for patients with human immunodeficiency virus (HIV) infection. This has led to reduction in acquired immunodeficiency syndrome (AIDS) related morbidity and mortality[1]. At present, antiretroviral drugs available in Malaysia include zidovudine, didanosine, lamivudine and stavudine which belong to the nucleoside reverse transcriptase inhibitor (NRTI) class. The two remaining classes include the non-nucleoside reverse transcriptase inhibitors (NNRTI) and the protease inhibitors (PI). The NNRTI class comprises of nevirapine and efavirenz. The PI class includes indinavir, ritonavir, saquinavir and nelfinavir. NRTIs may cause severe lactic acidosis and this is thought to be secondary to mitochondrial toxicity[2-3]. However, the incidence and prevalence may vary depending on the number and choice of NRTIs present in an antiretroviral regimen. In a longitudinal cohort study involving 2144 patients receiving NRTI therapy, the risk of symptomatic hyperlactataemia increased more than two fold for each additional NRTI used in a given regimen. Different combinations of NRTIs were also associated with different rates of symptomatic hyperlactataemia. The incidence was highest with the combination of stavudine and didanosine (59.4 cases per 1000 person years) and lowest with the combination of zidovudine and lamivudine (3 cases per 1000 person years). In a separate study, the incidence of symptomatic hyperlactataemia was calculated as 25.6 cases per 1000 person years for any regimen containing stavudine, as compared to 1.9 cases per 1000 person years for regimens without stavudine . As a result of these data, stavudine and didanosine combination as part of HAART regime is not preferred nowadays. In Malaysia, being a resource limiting country, the commonest regime used is stavudine, lamivudine and nevirapine. We report two patients who developed severe lactic acidosis related to NRTI.

CASE 1
A 34 year old HIV and Hepatitis B positive female patient had been on Lamivudine (3TC), Stavudine (D4T) and Efavirenz since 2002. The CD4 count in April 2005 was 130/mm^{3}. She became pregnant in February 2005 but failed to inform the physician on her April 2005 follow-up. She was referred from a public health clinic in June 2005 at 31 weeks of gestation with a one day history of abdominal pain, chest discomfort and shortness of breath. She was afebrile and haemodynamically stable.

Examination of the cardiorespiratory system and abdomen were unremarkable except for the gravid uterus. Investigations revealed profound metabolic acidosis with a pH of 6.87, pCO_2 13mmHg, HCO_3 2.0mmol/l and pO_2 130mmHg. Serum sodium was 133mmol/l, serum potassium 5.1mmol/l, serum chloride 97mmol/l and serum creatinine 0.12mmol/l. Serum amylase was 2017u/l, alanine aminotransferase (ALT) 51u/l and aspartate transaminase (AST) 148u/l. Creatinine kinase (CK) was 169u/l. Anion gap was 39.1mmol/l (normal range: 10-15mmol/l). Serum lactate was 13.7mmol/l (normal range: 0-5mmol/l). Toxicology screen was negative. She was managed in intensive care unit (ICU) with empirical antibiotics, intravenous infusion of sodium bicarbonate, oral riboflavin and pyridoxine. HAART therapy was stopped. She was mechanically ventilated six hours after admission with vasopressor support for haemodynamic instability. She developed oliguric acute renal failure (ARF) and upper gastrointestinal bleeding necessitating continuous renal replacement therapy (CRRT). Despite these measures, she succumbed 27 hours after admission from multiorgan failure.

CASE 2
A 31 year old HIV positive female patient had been on Efavirenz, D4T and 3TC since April 2004. The CD4 count in October 2005 was 350/mm^{3}. She presented to a private hospital in January 2006 with an acute abdomen and underwent laparoscopic cholecystectomy the next day. Ultrasonography of the abdomen had shown cholelithiasis. Post operatively the patient was tachypnoeic and was referred to our care when this persisted. On arrival to our surgical unit the next day she was drowsy, dehydrated and tachypnoeic. She was afebrile and haemodynamically stable.

Cardiorespiratory and abdominal examination was normal. Investigations revealed severe metabolic acidosis with pH 7.04, pCO_2 13mmHg, HCO_3 3.0mmol/l and pO_2 206mmHg. Serum sodium was 129mmol/l, serum potassium 3.2mmol/l, serum chloride 101mmol/l and serum creatinine 0.20mmol/l. Serum amylase was 232u/l. ALT was 60u/l and AST was 131u/l. CK was 367u/l. Anion gap was 28.2mmol/l. Serum lactate was 12.8mmol/l. Toxicology screen was negative. The patient was managed in ICU with mechanical ventilation, intravenous sodium bicarbonate and vasopressors. She went into oliguric ARF two days later and CRRT was initiated. The patient succumbed 12 hours later with multiorgan failure.

Symptoms
    Asthenia
    Muscular weakness
    Anorexia
    Weight Loss
    Fever or hypothermia
    Nausea and vomiting
    Abdominal pain
    Dyspnoea
Physical Examination
    Tachypnoea
    Hepatomegaly
Laboratory examination
    Elevated serum lactic acid concentration
    Low serum bicarbonate concentration
    Elevated transaminases
    Elevated amylase and lipase
    Elevated lactate dehydrogenase
    Elevated creatinine phosphokinase
Radiological examination
    Hepatomegaly and fatty infiltration of liver on ultrasound
Biopsy of tissue
    Hepatic biopsy: macrovacuolar and microvacuolar steatosis, ballooned mitochondria and loss of cristae
    Muscle biopsy: red-ragged fibers, lipid droplets, muscle fiber atrophy, abnormal mitochondrial architecture and decreased mitochondrial DNA

Fig. 1: Clinical features of lactic acidosis

DISCUSSION

Lactic acidosis due to NRTI is caused by mitochondrial toxicity. Impaired pyruvate oxidation, β-oxidation and dysfunction of mitochondrial DNA γ-polymerase leads to lactate production and accumulation. 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 in Kreb's cycle substrates and decreased adenosine triphosphate (ATP) production. Alternative energy sources through glycolysis are upregulated, which in addition to hepatic dysfunction, causes increase lactate levels.

Lactic acidosis can be divided into two broad categories- those with or without evidence of systemic impairment in tissue oxygenation, referred to as Type A and Type B lactic acidosis, respectively. Underlying causes of Type A lactic acidosis include hypoxaemia, cardiac arrest, and tissue hypoperfusion resulting from hypovolaemia, heart failure or sepsis. Both patients did not have any evidence on physical examination or laboratory investigations to suggest Type A lactic acidosis.

Therefore, a diagnosis of Type B lactic acidosis was considered. Type B lactic acidosis occurs as a result of deregulation of cell metabolism rather than impairment in tissue oxygenation. Causes of Type B lactic acidosis include inherited mitochondrial disease, such as respiratory chain enzyme deficiencies, and toxin induced impairment of mitochondrial function. Given that the patients did not have a previous history of inherited mitochondrial disease and was not on drugs like metformin, Type B lactic acidosis induced by NRTIs was suspected[5].

Severe Type B lactic acidosis is uncommonly associated with NRTI but carries a very high mortality rate of 33% and 57%. Higher lactate levels are associated with increased mortality. Asymptomatic hyperlactataemia may be found in up to 21% of NRTI treated patients. The incidence of symptomatic hyperlactaemia is lower at 1.3-20.9 per 1,000 treated patient years[2]. The relatively high incidence of asymptomatic mild hyperlactataemia that is unlikely to progress to the symptomatic state makes routine lactate monitoring in patients on NRTI unhelpful. However, serum lactate needs to be performed in patients presenting with symptoms suggestive of lactic acidosis.

Clinical manifestations of NRTI-induced lactic acidosis are subtle and non-specific. The commonest presenting symptoms are gastrointestinal in origin (Fig. 1). The gold standard for diagnosis is either muscle or liver biopsy but both are not routinely performed. Risk factors associated with NRTI-induced lactic acidosis include female sex, use of high dose didanosine (DDI) or D4T, impaired renal function, low nadir CD4 T-cell count prior to initiation of HAART, co-infection with hepatitis B or C, pregnancy, inherited mitochondrial dysfunction, obesity, liver failure and malnutrition. Age, duration of NRTI use and mild hyperlactataemia does not increase the risk of severe lactic acidosis[4]. Both patients had several risk factors for the development of severe lactic acidosis.

Management of severe lactic acidosis includes awareness of risk factors, early recognition of the syndrome and immediate discontinuation of NRTI. There has been no systematic studies on its treatment. The management remains supportive. Intravenous bicarbonate infusion, ventilatory support and bicarbonate based dialysis has been used. Other therapies include supplementation of cofactors, e.g. thiamine, riboflavin, L-carnitine, prostaglandin E and coenzyme Q[2].

CONCLUSION

HIV-infected patients with NRTI-induced lactic acidosis suffer a high mortality. Patients with risk factors associated with NRTI-induced lactic acidosis should use HAART with caution and with frequent close monitoring. Stavudine in particular should never be prescribed in pregnancy as the risk of lactic acidosis and mortality is very high. Management includes withdrawal of HAART and intensive supportive therapy. Symptomatic hyperlactataemia should be considered in the differential diagnosis of HIV-infected patients receiving HAART who are admitted to hospital with vague and non specific gastrointestinal symptoms.

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