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Fatal Toxicity from Symptomatic Hyperlactataemia

A Retrospective Cohort Study of Factors Implicated with Long-Term Nucleoside Reverse Transcriptase Inhibitor use in a South African Hospital

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Abstract

Background: In many Sub-Saharan African countries, first-line therapy for HIV may include a nucleoside reverse transcriptase inhibitor (NRTI). Long-term NRTI use is associated with symptomatic hyperlactataemia due to inhibition of mitochondrial DNA polymerase γ, a potentially fatal complication.
Objective: The purpose of the study was to evaluate the factors associated with inhospital fatality for HIV inpatients prescribed NRTIs long term who presented with symptomatic hyperlactataemia.
Methods: We performed a retrospective cohort study at a 900-bed university hospital in South Africa over 4 years (2005–2008). We included HIV inpatients prescribed NRTIs long term who presented with symptomatic hyperlactataemia (long-term NRTI use; lactate >4.0 mmol/L; absence of infectious source; symptoms requiring admission). Data included demographics, medical history, NRTI duration, blood pressure, symptom duration and relevant laboratory data.
Results: Of 79 patients who met inclusion criteria (mean age 38.2 ± 10.5 years, 97% female) there were 46 fatalities (58%). Factors significantly associated with fatality were presence of diabetes mellitus ($p = 0.04$), lactate ≥10 mmol/L ($p = 0.003$), pH <7.2 ($p = 0.002$), creatinine ≥200 μmol/L ($p = 0.03$) and altered mental status ($p = 0.03$).
Conclusions: In this study, NRTI-related symptomatic hyperlactataemia occurred predominantly in females. Mortality was associated with severely elevated lactate (≥10 mmol/L), the degree of acidosis, elevated creatinine, history of diabetes and altered mental status on presentation.

Background

The incidence of AIDS increased throughout the 1980s and peaked in the early 1990s, and has since steadily declined in the US but not in the rest of the world. The introduction of highly active antiretroviral therapy (HAART) may reverse the course of a disease that, if left untreated, invariably leads to death. Internationally, AIDS/HIV have wreaked havoc, particularly in Sub-Saharan Africa where two-thirds (67%) of the global total of 32.9 million people with HIV live and three-quarters (75%) of all AIDS deaths in 2007 occurred.[1] In recent years, through governmental and non-governmental bodies, antiretroviral treatments have delivered much-needed treatment for AIDS/HIV to many of the resource-limited countries in Sub-Saharan Africa. In particular, nucleoside reverse trancriptase inhibitors (NRTIs), such as stavudine and didanosine, are a mainstay of therapy in these settings because of their effectiveness and relative low cost.[2]

In South Africa, where an estimated 5.7 million people are infected with the AIDS virus, NRTIs are part of a first-line regimen of treatment of HIV.[1,3] Under the 2003 WHO guidelines for treatment of HIV, first-line therapy should consist of a non-NRTI and two NRTIs. Second-line therapy should consist of a ritonavir-boosted protease inhibitor plus two NRTIs.[2] Stavudine is a thymidine nucleoside analogue that is one of the cheapest and oldest NRTIs, which is thus often chosen in both first- and second-line HAART regimens in the Sub-Saharan African region.

NRTIs block viral replication by competing with cellular deoxynucleotide triphosphates for incorporation into proviral DNA, and are specific for HIV type 1 (HIV-1) reverse transcriptase.[4] However, NRTIs have also been found to bind to other human DNA polymerases such as human mitochondrial polymerase γ, which is responsible for mitochondrial DNA (mtDNA) replication. Inhibition of mtDNA impairs the synthesis of mitochondrial enzyme that generate adenosine triphosphate by oxidative phosphorylation, leading to a number of consequences, including myopathy,[5] lipoatrophy,[6] hepatic steatosis,[7] pancreatitis,[7] peripheral neuropathy,[8] hyperlactataemia and lactic acidosis.[9]

Lactic acidosis, a rare but serious side effect of NRTI use, typically occurs in the absence of hypoperfusion (type B lactic acidosis) as opposed to lactic acidosis from sepsis.[10] It is a condition that is often difficult to diagnosis because of vague presenting symptoms (e.g. fatigue, weakness, dyspnoea, tachycardia, unexplained weight loss, abdominal pain, nausea). There also exists a subset of patients who have asymptomatic hyperlactataemia on NRTI therapy but not lactic acidosis. Development of lactic acidosis usually follows a minimum of 6 months of treatment with antiretrovirals. Resolution of lactic acidosis even after cessation of the offending agent can vary between 4 and 28 weeks, and mortality is very high (33% for case series and 57% in a recent literature review).[11] Risk factors that are associated with developing this complication include female sex, pregnancy, use of stavudine and/or didanosine, prolonged HAART duration, obesity, reduced creatinine clearance and low-baseline CD4 count.[10,12-14] Treatment of lactic acidosis is predominantly supportive. There has been anecdotal success with thiamine,[15] riboflavin,[16] ubiquone,[17] biotin,[17] zinc picolinate,[17] N-acetylcysteine,[17] uridine,[17] and L-carnitine.[18] However, none of these measures are approved for the treatment of lactic acidosis related to NRTI therapy.

While risk factors for NRTI users to develop hyperlactataemia are reported, clinical predictors of adverse outcomes (e.g. mortality) are poorly described. We performed a retrospective study designed to derive clinical risk factors associated with inhospital fatality for HIV inpatients using NRTIs with symptomatic hyperlactataemia at a large Sub-Saharan hospital.

Methods

Study Design

This retrospective study was performed at Edendale Hospital, a 900-bed hospital in Pietermaritzburg, South Africa. Inpatient charts from 2005 to 2008 were reviewed for suitable

cases for our study. Cases were chosen on the basis of inpatient diagnosis of hyperlactataemia. This study was approved by the Institutional Review Boards at Mt Sinai School of Medicine and Edendale Hospital.

Selection of Patients

Eligible patients admitted to the hospital with HIV were treated with HAART and the majority were given either one of two regimens (left to the judgement of the treating physician), which, for simplicity, we will refer to as regimens IA, IB, 'other' (if a non-standard regimen was tailored to the patient) or 'unknown' (if chart documentation was insufficient to determine the exact regimen used). Regimen IA consisted of a triple therapy of stavudine, lamivudine and efavirenz, whereas regimen IB consisted of stavudine, lamivudine and nevirapine. Subjects were included in the study based on the presence of NRTI-related hyperlactataemia, defined as long-term use of the NRTIs stavudine and/or didanosine, initial lactate >4.0 mmol/L, absence of infectious source other than HIV/AIDS, absence of diabetic ketoacidosis, absence of liver failure, and symptoms requiring hospital admission. Long-term NRTI use is >6 months on a single regimen. Exclusion criteria included incomplete follow-up (inter-hospital transfer or no outcome data) and age <18 years.

Data Collection

Paper charts were reviewed by a single, trained reviewer. Data included demographics, medical history, NRTI duration, blood pressure, symptom duration (including any symptom involved in acute presentation to the hospital), clinical mental status (altered mental status defined as Glasgow Coma Score <15) and relevant laboratory data (serum lactate, A-a gradient [i.e. alveolar-arterial oxygen gradient], anion gap, white blood cell count, CD4 count and creatinine level). The A-a gradient, a measure of the degree of hypoxaemia, was calculated in standard fashion using the following equation (equation 1):

$$\left[Fi_{O_2} * \left(P_{atm} - P_{H_2O}\right) - \left(Pa_{CO_2}/0.8\right)\right] - Pa_{O_2} \quad \text{(Eq. 1)}$$

where Fi_{O_2} is the fraction of inspired oxygen, P_{atm} is atmospheric pressure, P_{H_2O} is water partial pressure, Pa_{CO_2} is arterial partial pressure of carbon dioxide, and Pa_{O_2} is arterial partial pressure of oxygen. Serum creatinine (Cr) levels are a measure of renal function. Generally, serum creatinine levels of <140 μmol/L signify normal renal function, whereas Cr levels of >140 μmol/dL indicate decreased renal function. A venous lactate sample (with lactate measured in mmol/L) was initially obtained in the Emergency Department. Subsequent blood samples for lactate assessment were drawn during inpatient admission when clinically indicated according to the treating physician. The primary outcome was all-cause inhospital fatality. The study endpoint was discharge from the hospital or inpatient mortality.

Data Analysis

Descriptive statistics included means (with standard deviation) for continuous data and percentages for categorical data. Categorical and continuous variables were compared between groups using the chi-squared (or Fischer exact test when there were less than five subjects in one cell of any 2×2 comparison table) and t-test, respectively. Normality of variables was verified using the Shapiro-Wilk test; p-values <0.05 were considered to be statistically significant. Univariate odds ratios with 95% confidence intervals were calculated for characteristics associated with fatality. All computer analyses were performed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA).

Results

We enrolled 87 patients who met the inclusion criteria, and excluded eight patients because of incomplete follow-up (two inter-hospital transfers and six lost to follow-up), leaving 79 patients for analysis. All deaths occurred within a period of 2 weeks after hospital admission. Of the 79 patients, 76 were female (97%) and the mean age was 37.8 years (range 22–68 years). Most of the patients were on either regimen IA (n = 55) or IB (n = 11), both of which contain stavudine. Chronic

co-morbidities included (in order of prevalence) tuberculosis, hypertension, diabetes mellitus, seizure disorder, prior stroke, asthma and coronary artery disease. The only co-morbidity statistically associated with fatality was diabetes ($p = 0.04$). Baseline characteristics are summarized in table I.

Clinical characteristics of patients analyzed in this study that were potentially correlated with hyperlactataemia are summarized in table II. Factors without a statistical association ($p > 0.05$) with mortality were age >35 years, use of regimen IA (stavudine/lamivudine/efavirenz), NRTI use of more than 6 months, symptom duration of more than 5 days and CD4 count of <100 cells/μL. Laboratory values found to be predictive of mortality included serum lactate concentration ≥4 mmol/L ($p = 0.002$) or ≥10 mmol/L ($p = 0.003$), creatinine concentration ≥200 μmol/L (0.03) and pH <7.2 ($p = 0.002$). Presence of altered mental status (defined as Glasgow Coma Score <15) was significantly associated with mortality ($p = 0.03$). In contrast, measurements of neither systolic blood pressure, diastolic blood pressure nor mean arterial pressure on presentation were found to be associated with mortality ($p > 0.05$).

Discussion

In this study, factors most associated with fatality from NRTI-related hyperlactataemia were severely elevated serum lactate, decreased pH, elevated serum creatinine, diabetes and altered mental status on hospital admission. In contrast to previous studies,[12] age was not associated with mortality. These findings build upon prior data and warrant future study in select populations to help prevent morbidity and mortality for patients taking long-term NRTI therapy, especially women receiving treatment in Sub-Saharan Africa.

Table I. Baseline characteristics of patients. Description of the study population (n = 79) and univariate analysis: demographics, HIV/AIDS history and co-morbidities

Characteristics	Overall	Fatalities	Survivors	p-Value
Demographic				
Females [n (%)]	76 (97)	45 (98)	31 (97)	1
Mean age [y; mean (± SD)]	37.8 ± 10	37.2 ± 10	38.3 (± 10)	0.68
Age >35 y [n (%)]	35 (44)	19 (41)	16 (53)	0.3
HAART regimen [n (%)][a]				
IA	55 (70)	31 (67)	24 (43)	0.7
IB	11 (14)	6 (13)	5 (45)	1
Other	3 (4)	1 (2)	2 (6)	1
Unknown	10 (13)	8 (17)	2 (6)	NA
Co-morbidities [n (%)]				
Tuberculosis	15 (19)	8 (17)	7 (21)	0.77
Hypertension	7 (9)	6 (13)	1 (3)	0.23
Diabetes melllitus	6 (8)	6 (13)	0 (0)	0.04[b]
Seizure disorder	2 (3)	1 (2)	1 (3)	1
Prior stroke	2 (3)	1 (2)	1 (3)	1
Pregnancy	3 (4)	3 (7)	0 (0)	1
Asthma	1 (1)	1 (2)	0	1
Coronary artery disease				
Total	79	46	32	NA

a p-Values for HAART regimen (IA, IB, other) were calculated for each regimen versus the other two as the comparison group (e.g. IA vs the combination of 'IB plus other').

b Significant p-value.

HAART = highly active antiretroviral therapy; **IA**/**IB** = HAART regimens (regimen IA = stavudine/lamivudine/efavirenz; regimen IB = stavudine/lamivudine/nevirapine); **NA** = not applicable.

Table II. Clinical factors correlated with inhospital fatality[a]

Clinical characteristic	Survivors	Fatalities	p-Value	Univariate OR (95% CI)
Regimen IA (n)[b]	24/31	31/38	0.67	1.3 (0.4, 4.2)
NRTI treatment for ≥6 mo (n)	20/28	26/40	0.58	0.74 (0.26, 2.1)
Symptom duration ≥5 d (n)	12/33	17/46	1	1.03 (0.4, 2.6)
CD4 count <100 (cells/μL) [n]	3/6	5/13	1	0.6 (0.1, 4.4)
Absolute lactate (mmol/L) [mean ± SD]	7.0 ± 3	11.0 ± 4.5	<0.001[c]	
Lactate ≥10 (mmol/L) [n]	7/32	24/43	0.003[c]	4.5 (1.6, 12.7)
Lactate ≥4 (mmol/L) [n]	23/32	42/43	0.002[c]	16.4 (1.9, 137)
pH <7.2 (n)	4/28	22/42	0.002[c]	6.6 (1.9, 22.3)
Creatinine (μmol/L) [mean ± SD]	57.4 ± 11.2	119 ± 20.8	0.02[c]	NA
Creatinine ≥200 (μmol/L) [n]	1/26	9/33	0.03[c]	9.4 (1.1, 79.7)
A-a gradient ≥10 (n)	4/28	6/37	1	1.2 (0.3, 4.6)
GCS [mean ± SD]	15.0 ± 0	13.7 ± 3.1	0.05[c]	NA
Altered mental status (GCS <15) [n]	0/17	7/24	0.03[c]	∞

a Univariate analysis of clinical factors related to inhospital fatalities.

b Regimen IA = stavudine/lamivudine/efavirenz.

c Significant p-value.

A-a = alveolar-arterial (see Methods section for calculation); **GCS** = Glasgow Coma Score; **NA** = not applicable; **NRTI** = nucleoside reverse transcriptase inhibitor; **OR** = odds ratio; ∞ indicates infinity.

The majority of patients were treated for their HIV with either of two regimens – regimen IA (stavudine/lamivudine/efavirenz) and regimen IB (stavudine/lamivudine/nevirapine), both of which are first-line regimens, consisting of a non-NRTI and two NRTIs. Efavirenz, which is found in regimen IA, is a teratogen and is thus not recommended for women who are pregnant or who are planning to conceive.[19] Nevirapine has a wide toxicity profile, consisting of hepatotoxicity and Stevens-Johnson syndrome.[20] Stavudine is a thymidine nucleoside analogue that is phosphorylated intracellularly to the active metabolite, stavudine 5′-triphosphate. This metabolite inhibits HIV replication, either by competing with thymidine 5′-triphosphate for incorporation into viral DNA by reverse transcriptase or by causing premature termination of the viral chain after incorporation. *In vitro* studies implicate the active moiety, stavudine 5′-triphosphate, to be responsible for the depletion of mtDNA via inhibition of mitochondrial DNA polymerase γ.[21] Stavudine is no longer used in North America as new agents with less toxic side effects have been developed.

The sex ratio of cases of lactic acidosis secondary to HAART therapy was overwhelmingly skewed towards females (76 : 3). This finding is in concordance with prior studies.[11,12,22] Demographics can contribute to this disparity as more women in Sub-Saharan Africa are infected with HIV. Together with the higher prevalence rates in women and prevention of mother-to-child transmission initiatives, African women are more likely to be placed on HAART than males. Since dosing is fixed, biological factors such as fat composition, hormonal secretion, body mass index (BMI) and drug metabolism may also be proposed to explain the great disparity in prevalence of NRTI-induced lactic acidosis between men and women.

Because the mechanism of NRTI-induced lactic acidosis is mitochondrial toxicity, and mitochondria are solely inherited via the maternal line, it follows that men should not have greater genetic risk to develop mitochondrial toxicity than women. Thus, one explanation for our findings may instead be related to relative drug concentrations in the blood. As the dose of NRTI is the same (30 mg twice daily for patients <60 kg and 40 mg twice daily for those >60 kg) irrespective of sex, it follows that women, who are generally smaller and have less muscle than men, may be receiving higher doses per kilogram. Unfortunately, our data did not allow for BMI analysis and this should be the topic of future investigations.

However, one cannot help but postulate whether there is a threshold for NRTI-induced lactic acidosis with chronically higher serum concentrations of NRTI. One implication of this would be that women might conceivably benefit from weight-based dosages of NRTIs. Further investigation into this matter is warranted.

Altered mental status, which we defined as a Glasgow Coma Score of <15, was found to be significantly associated with mortality. The pathophysiology of altered mental status in NRTI-induced lactic acidosis may be multifactorial. As in sepsis, where lactate is also a marker of severity, microcirculatory abnormalities, altered blood-brain barrier permeability and inflammatory cytokines may all play a role in the development of toxic-metabolic encephalopathy.[23]

As *a priori*, one might assume that HIV severity (e.g. CD4 count) or clinical symptoms (e.g. duration, vital signs, length of therapy) might predict fatality in NRTI-induced lactic acidosis. In contrast, we found that CD4 count, symptom duration, initial vital signs and length of NRTI therapy were not associated with fatality. Since CD4 count is a surrogate for disease burden and immunosuppression, the results imply that severity of HIV is not a factor in developing lactic acidosis. However, viral load was not included in this study, which is a more direct marker of HIV severity. In addition, only a small number of patients had known CD4 count, thus skewing our results. The lack of correlation between length of NRTI therapy and mortality suggests that there is no length of time while taking NRTI therapy that guarantees protection from lactic acidosis and that a genetic component does not play a role in developing lactic acidosis. Thus, any patient taking NRTI therapy is at risk for developing lactic acidosis at any time during their treatment course. Routine screening, however, has proven not to be useful for patients on HAART regimens.[24]

As NRTI therapy becomes more prevalent in sub-Saharan Africa, there may be a future rise in the incidence of NRTI-induced lactic acidosis. Based on this study, we recommend that alternative HAART regimens be substituted for the current first-line regimen in selected populations. Screening for risk factors and hyperlactataemia may lead to reasonable substitutions that may include other drugs that have a lower incidence of adverse effects, such as lamiduvine, abacavir and tenofovir. Policy-makers and pharmaceutical companies should consider providing recommendations for drug screening and algorithms for alternative drugs as substitution for staduvine and didanosine.

Limitations

When interpreting this study, several limitations must be kept in mind, including all the limitations and biases of a retrospective, single-centre study design. A disproportionate amount of women were included in the study, which may reflect selection bias or inadequate screening of men. However, we feel the sex bias was more a function of the increased prevalence of the disease progression in women. Genotyping for mtDNA was not performed, which may have shed light into this sex difference. BMI, noted in previous studies to be a factor in developing NRTI-induced lactic acidosis, was not included in the analyses because the information was not available. HIV-RNA viral load was also not available for analysis. The inclusion of viral load would have shed light on the role of HIV in the development of lactic acidosis. While we derived several univariate predictors of fatality, because of the unfortunately high amounts of missing data from the source database a multivariate statistical analysis was not possible because of resultant listwise deletion of all but 16 cases. Additionally, CD4 count was recorded for a minority of patients (n = 8), insufficiently powering the study to lead to any conclusions about CD4 count and its role in the course of fatal lactic acidosis. Furthermore, the population only included South Africans and thus generalizability issues may be applicable.[3]

Conclusions

Symptomatic hyperlactataemia due to long-term NRTI use occurred largely in females and was associated with high inhospital mortality. The factors associated with mortality included severe serum lactate elevation, decreased serum

pH, elevated serum creatinine, diabetes and altered mental status. We recommend aggressive management for patients with these high-risk features. We also recommend use of antiretrovirals with safer drug profiles in selected high-risk populations.

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