Lactic acidosis, risk factors and predictive laboratory markers: a nested case control study in South Africa

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Abstract

Background: The incidence of antiretroviral therapy (ART)-induced lactic acidosis and its associated mortality may be reduced by appropriate dosing, risk stratification and early detection.

Objectives: To describe the epidemiology of lactic acidosis, define the risk factors and identify predictive laboratory markers in the context of the roll-out of ART in South Africa.

Design: A nested case control study. Risk factor analysis was adjusted for the established risk factors of weight and gender.

Setting and subjects: Persons commenced on stavudine-containing therapy between 2004 and 2007 at Port Shepstone Hospital in KwaZulu-Natal were included. Persons with a body weight above 60 kg received Stavudine 40 mg twice daily, and those with a body weight below 60 kg, 30 mg twice daily.

Outcome measures: Assessed risk factors included weight, gender, age, alanine transaminase (ALT), urea, creatinine, albumin, cholesterol, triglyceride (TG) levels, CD4 counts and viral loads.

Results: Lactic acidosis occurred in 79 (17 per 1 000 person-years) of 1 762 people living with HIV on ART. Significant factors were being female [adjusted odds ratio (AOR) of 5.4] and increased body weight (adjusted OR of 1.1 per kg). The risk of lactic acidosis increased 6.6, 6.9 and 95 times (adjusted ORs) as weight increased from a baseline weight of < 60 kg to 60-69 kg, 70-79 kg or > 80 kg, respectively. Six months into therapy, predictors of developing lactic acidosis were an ALT > 50 IU/l (adjusted OR of 11.1) and a higher TG (adjusted OR of 8.8 per mmol/l). No associations were found with regard to age, CD4 count, viral load, and creatinine or albumin levels.

Conclusion: Obese females are at greatest risk of lactic acidosis, with an exponential increase in risk above 80 kg. The 30-mg dose may be preferable, given that a sharp increase in risk occurred at 60 kg, was most likely dose related, and that 30 mg has been shown to provide adequate virological suppression. Additional risk factors for lactic acidosis include a high ALT and TG levels at treatment.

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Introduction

South Africa has one of the highest human immunodeficiency virus (HIV) prevalence globally (11% in 2008). KwaZulu-Natal is the worst affected province (16%).[1] Drug toxicity is a major challenge when prescribing antiretroviral therapy (ART). Recent studies in South Africa reported incidence rates of lactic acidosis of 11-19 per 1 000 person-years,[2-4] higher than the 0.6-10 per 1 000 person-years reported in high-income countries.[5,6]

ART-related lactic acidosis, hyperlactataemia, peripheral neuropathy, lipodystrophy, hepatic steatosis and pancreatitis[7] are thought to result from mitochondrial dysfunction due to nucleoside reverse transcriptase inhibitors (NRTIs) interfering with human mitochondrial DNA polymerase γ enzyme activity.[6] Lactic acidosis is the most serious of the toxic effects, with a case fatality of 33-60%.[5] The risk of lactic acidosis is not equal across all NRTIs. The effect is greatest with didanosine, which is > stavudine > zidovudine > abacavir = lamivudine = tenofovir.[8] Stavudine is still widely used in South Africa and in low-income countries.

Established risk factors for lactic acidosis include being of the female gender, having a high body mass index (and weight), and duration of therapy (between six and

18 months).[2-4] Other drug-induced toxic effects, such as peripheral neuropathy and lipodystrophy, and a raised alanine transaminase (ALT), have been associated with the development of lactic acidosis.[3,9] Recent controlled studies provide conflicting evidence with regard to other risk factors for lactic acidosis, such as increased age, impaired renal function, low serum albumin and a low CD4 count.[3,10]

The first objective of this study was to describe the demographic, clinical and biochemical features of persons presenting with lactic acidosis. The subsequent objective was to determine the clinical and laboratory factors that might predict the development of lactic acidosis prior to commencement of ART, and while on ART (early warning signs), and therefore define a category of patients at particular risk of developing lactic acidosis.

Method

Setting

The study was conducted at Port Shepstone Hospital in KwaZulu-Natal, which serves a semi-rural population. Adult persons living with HIV with a CD4 count less than 200 cells/µl, or World Health Organization stage 4 disease (acquired immune deficiency syndrome-defining criteria) routinely received twice-daily stavudine 40 mg if they weighed over 60 kg, or 30 mg if they weighed less than 60 kg up to July 2007, after which all patients received 30 mg combined with lamivudine and either nevirapine or efavirenz. Zidovudine was usually substituted for stavudine when severe stavudine toxicity occurred. The investigations were performed at an on-site laboratory, excepting the HIV viral load estimations.

Study design

The incidence and nature of stavudine toxicity was described using a retrospective cohort of persons living with HIV (> 18 years) commenced on stavudine-containing ART from July 2004 to April 2007, and followed until November 2008. A matched case control study was nested within this cohort to determine the risk factors for lactic acidosis.

Cases

Lactic acidosis cases had to have completed at least four months of ART and to have presented with symptoms of hyperlactataemia (unexplained weight loss, loss of appetite, abdominal pain, abdominal distension, nausea or shortness of breath). Serum lactate had to be ≥ 5 mmol/l and serum CO_2 or standard bicarbonate ($SHCO_3$) < 20 mmol/l.[2,3,10] If the lactate was above normal (> 2.5 mmol/l), but did not fulfil the biochemical criteria for lactic acidosis, then a diagnosis of symptomatic hyperlactataemia was made. Potential lactic acidosis cases who also had another possible cause of lactic acidosis, such as diabetic ketoacidosis, dehydration, sepsis and renal failure, were excluded.

Controls

Controls had to have completed at least 15 months of ART, and not to have developed any stavudine-related toxicity that required its discontinuation. Controls were matched with lactic acidosis cases according to the period of ART commencement to ensure equal duration of drug exposure.[3] This also reduced bias that might have been caused by the evolving state of knowledge on the diagnosis and management of stavudine-induced lactic acidosis.

Data collection and analysis

Baseline data were extracted from the hospital's electronic register. Cases presenting with stavudine-induced lactic acidosis were identified from pharmacy, admission and mortuary records. A retrospective chart review was performed on all cases and controls.

Statistical analysis

Conditional logistic regression modelling was used to compare exposure variables between cases and controls. Analysis was controlled for weight and gender. A p-value of < 0.05 was considered to be significant. Approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, the provincial Department of Health and hospital management.

Results

Description of entire cohort

A total of 1 762 adult patients (mean age of 36.1 years, mean baseline CD4 count 113 cells/µl) were initiated on stavudine-containing ART from August 2004 to April 2007. Baseline cohort characteristics, based on gender and weight categories, are shown in Table I. Follow up, until November 2008, included 4 566 person-observation years.

Incidence of stavudine toxicity

Stavudine-induced toxicity requiring a drug substitution occurred in 275 (60 per 1 000 person-years) persons with HIV and commenced on ART. Lactic acidosis occurred in 79 (17 per 1 000 person-years). The highest incidence was females > 90 kg (109 per 1 000 person-years) (Table II).

Spectrum of clinical presentation and mortality of lactic acidosis

In the 63 cases with lactic acidosis and complete records, 59 (94%) presented with weight loss (a median loss of 6 kg, interquartile range of 4-8 kg), 45 (71%) with abdominal symptoms (nausea, anorexia, pain or distension), 15 (24%) with peripheral oedema and 8 (13%) with dyspnoea. Peripheral neuropathy was recorded in 44 (56%) and lipodystrophy in 35 (42%) cases. Weight loss was the only presenting symptom in 13 (21%) and a combination of weight loss and abdominal symptoms occurred in 43 (68%) cases. Lactic acidosis took place after between eight

Table I: Baseline characteristics of adults commenced on stavudine-containing antiretroviral therapy between 2004 and 2007 at Port Shepstone Hospital, categorised according to gender and weight (n = 1 762)

Gender	(n)	%	Mean age (years)	Mean weight (kg)	Mean CD4 (cells/ul)	Mean Hb (g/dl)
Females	1 226	69.5	35.4	60.6	113	11.2
< 60 kg	583	33.7	35.1	51.2	96	10.8
60-69 kg	359	20.8	35.2	64	128	11.5
70-79 kg	117	6.8	36.2	74	125	11.7
> 80 kg	99	5.7	36.1	88.5	144	12.1
Weight unknown	68					
Males	536	31	37.8	60.9	114	11.3
< 60 kg	244	14.1	37.2	51.5	101	11
60-69 kg	164	9.5	37.9	63.9	113	11.4
70-79 kg	56	3.2	38.1	74	123	11.5
> 80 kg	40	2.3	39.6	87.2	154	12.3
Weight unknown	32					
Total	1 762	100	36.1	60.7	113	11.2

Hb: haemoglobin

Table II: The incidence and type of stavudine toxicity in adults commenced on antiretroviral therapy between 2004 and 2007 at Port Shepstone Hospital (n = 1 762)

Toxicity	n	Total	Incidence per 1 000 person-years (95% CI)
Lactic acidosis	79	1 762	17 (14 to 21)
Females*	72	1 225	23 (18 to 28)
< 40 kg	1	24	16 (-15 to 47)
40-49 kg	4	175	9 (0 to 17)
50-59 kg	9	383	9 (3 to 15)
60-69 kg	26	359	28 (18 to 38)
70-79 kg	9	117	30 (11 to 48)
80-89 kg	12	76	69 (34 to105)
> 90 kg	9	32	109 (48 to 167)
Males	7	536	5 (1 to 9)
< 60 kg	2	244	3 (-1 to 8)
60-69 kg	1	164	2 (-2 to 7)
70-79 kg	2	56	14 (-5 to 32)
> 80 kg	2	40	19 (-7 to 46)
Symptomatic hyperlactataemia	84	1 762	19 (15 to 22)
Peripheral neuropathy	67	1 762	15 (11 to 18)
Lipodystrophy	43	1 762	9 (7 to 12)
Pancreatitis	2	1 762	0 (0 to1)
Total	275	1 762	60 (54 to 67)

CI: confidence interval
*: n = 1 729 (total subjects with known weights)

and 16 months' treatment duration in the majority (67/79, 85%) of cases (a median of 10 months, and a range of 5-24 months).

The median serum lactate was 7.5 mmol/l (a range of 5-11.7), and mean serum CO_2 of 17 (a range of 0-19), of which 21 of 79 (27%) had lactate > 10 mmol/l or serum CO_2 < 15 mmol/l). In a subgroup of 65 cases who had a blood gas analysis, 49 (75%) had a pH < 7.34 and 11 (17%) a pH < 7.2.

Overall mortality from lactic acidosis was 7.6% (6/79). The cases who died had a lactate of > 10 mmol/l. Of the patients with lactate > 10, 40% (6/15, 40%) died. Seventy-five per cent (6/8) of cases with a serum CO_2 < 15 mmol died. All of the cases with a serum CO_2 < 10 mmol/l died. Fifty-five per cent (6/11) of patients with a pH < 7.2 and 83% (5/6) with a pH < 7.1 died. Four cases of lactic acidosis occurred during pregnancy. All of these patients survived. Three pregnancies were carried to term. The babies were born alive and well. There was one intrauterine death.

Patients with stavudine toxicity were changed from stavudine to zidovudine without recurrence of lactic acidosis during the follow-up period.

Comparison between lactic acidosis cases and controls at baseline

The clinical characteristics of cases with lactic acidosis and matched controls were compared at baseline (Table III). Female gender and weight were the only two parameters that emerged to have a statistically significant difference. As the baseline weight category of cases increased from < 60 kg, the risk of developing lactic acidosis increased significantly. When the weight increased to 60-69 kg,

Table III: Description and matched analysis of baseline characteristics between cases with lactic acidosis and matched controls (n = 79)

Characteristics	Description of groups				Matched analysis of pairs, adjusted for gender and weight		
	Cases with lactic acidosis		Matched controls (no lactic acidosis)		n*	p-value	Adjusted OR (95% CI)
	Mean	%	Mean	%			
Age (years)	35.8		35.9		70	0.929	1 (0.9 to 1.1)
Female gender		91.1		70.5	70	0.006	5.3 (1.6 to 17.8)
Efavirenz regimen		51.8		53.2	70	0.881	0.9 (0.3 to 2.6)
Previous antiretroviral drugs		12.7		6.3	70	0.371	0.7 (0.3 to 1.5)
Diabetes		3.8		1.3	69	0.625	**
Currently pregnant		5.1		0	68	**	**
Hepatitis B surface antigen positive		9.1		12.2	16	0.883	1.1 (0.3 to 4.4)
Weight (kg)	70.2		57		69	0.001	1.1 (1.1 to 1.2)
CD4 (cells/µl)	126		113		70	0.677	1 (1 to 1)
Viral load (copies/ml)	167 850		181 2968		29	0.446	1 (1 to 1)
Haemoglobin (g/dl)	11.3		11.3		66	0.167	0.9 (0.7 to 1)
Alanine transaminase (IU/l)	30		26		60	0.511	1 (0.9 to 1)
Amylase (U/l)	149		183		19	0.534	1 (0.9 to 1)
Albumin (g/l)	34		32		56	0.338	0.9 (0.90 to 1)
Urea (mmol/l)	3.52		3.69		54	0.353	1.1 (0.89 to 1.5)
Creatinine (µmol/l)	81		77		54	0.954	1 (0.9 to 1)
Cholesterol (mmol/l)	3.6		3.6		52	0.919	0.9 (0.6 to 1.7)
Triglycerides (mmol/l)	1.3		1.2		52	0.125	1.7 (0.9 to 3.3)

CI: confidence interval, OR: odds ratio
* Only pairs with results were considered for the analysis
**: McNemar's chi-square test could not be computed as a low conditional logistic regression model could not be achieved owing to the small sample size

Table IV: Characteristics of cases and controls six months into antiretroviral therapy (n = 79)

Characteristics	Description of groups				Matched analysis of pairs, adjusted for gender and weight		
	Lactic acidosis cases		Matched controls		n*	p-value	Adjusted OR (95% CI)
	Mean	%	Mean	%			
CD4 (cells/ul)	253		267		56	0.220	1 (1 to 1)
Log viral load)** (copies/ml)	630		18 096		47	0.488**	1 (1 to1)
Haemoglobin (g/dl)	12.9		13.3		57	0.221	0.8 (0.6 to 1.1)
Alanine tranaminase (IU/l)	44		33		52	0.029	1 (1 to 1.1)
> 50 IU/l		30.2		9.2		0.015	11.1 (1.6 to 77.7)
Amylase (U/l)	140		175		15	0.277	0.9 (0.9 to 1)
Urea (mmol/l)	3.5		3.6		55	0.828	1.1 (0.7 to 1.6)
Creatinine (umol/l)	74		73		55	0.806	1 (1 to 1)
Cholesterol (mmol/l)	4.5		4.2		51	0.111	1.6 (0.9 to 2.8)
Triglycerides (mmol/l)	1.41		0.88		52	0.039	8.7 (1.1 to 67.1)

CI: confidence interval, OR: odds ratio
*: Only matched pairs with results were considered for the analysis
**: Log value used in the analysis

70-79 kg and > 80 kg, risk (OR adjusted for gender) were 6.6 [95% confidence interval (CI) of 1.7-25, p-value 0.006], 6.9 (95% CI: 1.4-34.3, p-value 0.018) and 95.5 (95% CI: 6.9-1 384, p-value 0.001) respectively.

Comparison of cases and controls six months after commencement of antiretroviral therapy

The clinical characteristics and associations between cases with lactic acidosis and matched controls were again compared six months into ART (Table IV). Higher ALT or

triglycerides (TGs) were significantly associated with lactic acidosis. ALT was > 50 IU/l in 30% of cases, compared to only 9% of controls. Sixty-eight per cent of cases (19/28) with an ALT > 35 IU/l presented before 11 months on ART, compared to 35% (9/26) after 11 months (OR 3.4, p-value 0.034).

The risk (OR adjusted for weight and gender) of a case versus a control having a TG level at six months (exposure) of 0.5-1 mmol/l, 1.1-1.5 mmol/l and > 1.5 mmol/l, relative to those with TG < 1 mmol/l, were 3.9 (95% CI: 0.7-21.3, p-value 0.117), 11.2 (95% CI: 1.1-118.6, p-value 0.043) and 4.9 (95% CI: 0.2-103.2, p-value 0.311), respectively. There was no correlation between the ALT and TGs (Spearman's rank correlation coefficient 0.083, p-value 0.372).

Discussion

In this study, we confirmed the increased incidence of stavudine-induced lactic acidosis in South Africa, better defined associated risk factors, and also proposed laboratory markers that may have the potential to help to predict lactic acidosis.

Baseline risk factors

This study confirmed female gender and a high body weight to be strong risk factors for lactic acidosis (Table III).[2-4] The relationship with weight, particularly in females, appears to be complex (Table II). A sudden increase in incidence was observed when the baseline weight exceeded 60 kg, followed by an exponential increase when the baseline weight was more than 80 kg. It could be postulated that the first increase in incidence was attributed to the escalation in the dose of stavudine since it coincided with the recommended dose adjustment at 60 kg, and also because mitochondrial toxicity has been shown to be dose related.[9] The further increasing incidence above 80 kg, although the numbers were small in the higher-weight categories, was consistent with other studies,[10] and is likely to be owing to other weight-related factors.

Other factors considered to confer increased risk of developing lactic acidosis, such as age, CD4 count, renal function and albumin levels, did not emerge as risk factors in our study. Our findings were in keeping with others in the literature.[3]

The consistently higher incidence of lactic acidosis in developing countries compared to that in high-income countries remains an enigma. Possible explanations include the fact that females are markedly under-represented in in high-income country studies (26% in the Swiss cohort study),[11] and that female obesity is less common in such countries[12] compared to South Africa.[13] Encouraging patients in South Africa to tolerate other stavudine-related toxic effects owing to limited treatment alternatives may have facilitated further mitochondrial toxicity to the extent that lactic acidosis developed. This is supported by a high percentage of lactic acidosis cases in which other manifestations of mitochondrial toxicity were present. Other factors to be considered are genetic and the use of herbal medication which may potentiate stavudine toxicity directly or through drug interactions.

The predictive value of laboratory markers six months into antiretroviral therapy

Considering the late onset of lactic acidosis, which was confirmed in this study to occur between six and 18 months,[3] laboratory marker risk indicators, which are only apparent at six months into ART, may serve as useful and timely flags. This study showed that even after adjustment for gender and weight, ALT and TG levels at six months were significantly higher in cases (Table IV). The rise in ALT may be a manifestation of early stavudine-induced steatohepatitis.[3,6] This was underscored by the fact that patients with raised ALT at six months tended to present sooner with lactic acidosis.

The increased risk of lactic acidosis in patients with elevated TGs at six months, albeit within the normal range (Table IV), was not surprising when it is considered that elevated TGA levels have been associated with hyperlactataemia.[14] It was of interest that there was no correlation between the increase in ALT and TG levels. These findings need confirmation and further study by other investigators.

Mortality and early lactic acidosis identification

The mortality in this study was unusually low. This may be ascribed to enhanced clinical vigilance with the early detection of lactic acidosis. Weight monitoring appeared to be useful. The recognised associations of mortality, such as the level of lactate and severity of metabolic disturbance upon presentation, were also observed here.

Limitations of the study

As this was a retrospective study, we had to contend with incomplete recordkeeping. Body mass index could not be calculated since height was not measured.

Conclusion and recommendations

This study confirms the increased risk of lactic acidosis in patients on stavudine in a resource-limited setting. Obese females are at greatest risk. The 30-mg dose may be preferable given that efficacy has been demonstrated at lower doses.[15] Additional risk factors for lactic acidosis include high ALT and TG levels at treatment, but this needs further evaluation. The presence of other stavudine-related toxicities and weight loss might predict increased risk or onset of lactic acidosis.

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