Investigation of the effect of Stalanev (Stavudine, Lamivudine and Nevirapine) treatment on plasma lactate levels in adults attending Beatrice Road and Wilkins Infectious Diseases Hospital Opportunistic Infections Clinics in Harare, Zimbabwe

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Abstract

Main Objective: To evaluate the effect of Stalanev (Stavudine, Lamivudine and Nevirapine) treatment on plasma lactate levels in adults attending Beatrice Road Infectious Diseases Hospital and Wilkins Infectious Diseases Hospital Opportunistic Infections Clinics in Harare,
Design: Prospective cohort study carried out between January and May 2011
Setting: Beatrice Road and Wilkins Infectious Diseases Hospital Opportunistic Infections Clinics in Harare, Zimbabwe.

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Participants: A convenience sample of 180 ART naive HIV infected adults aged 20-68 years who were about to be initiated on STALANEV were recruited.
Results: The mean plasma lactate at baseline was 1.57 mmol/L (SD 0.43). After two months on STALANEV, 25 participants (13.9%) had hyperlactatemia and the mean plasma lactate level was 1.99mmol/L (SD 0.49). At four months follow up, 98 participants (54%) had hyperlactatemia and the mean plasma lactate level was 2.65 mmol/l (SD 0.55). Mean plasma lactate levels increased significantly from baseline to 2months follow up and from 2months follow up to 4months follow up ($p<0.001$). None of the participants developed lactic acidosis (plasma lactate >3.5) after two months of follow up but 14 (7.8%) developed mild lactic acidosis and three (1.7%) had moderate lactic acidosis after four months on STALANEV
Conclusions: Our findings are in agreement with those of other studies that reported that treatment with STALANEV leads to hyperlactatemia thereby posing a risk for the development of lactic acidosis in patients. In the absence of alternative regimens, we recommend routine monitoring of plasma lactate levels on all patients on STALANEV in Zimbabwe.

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Background

HIV/AIDS has become a significant public health problem in Zimbabwe, threatening the socio-economic fibre of the country and placing a tremendous strain on health delivery capacity. Although antiretroviral therapy (ART) roll out has reduced morbidity and mortality due to HIV/ AIDS, new challenges have arisen because of the development of metabolic changes induced by ART. These include impaired glucose metabolism, insulin resistance, lactic acidosis, osteopenia and dyslipidaemia[1]. Stavudine has been reported to cause mitochondrial toxicity that manifests as lactic acidosis in the majority of patients.[2]

Consequent to these adverse events, the WHO has recommended phasing out of stavudine in all ART regimens.[3] However, the stavudine-containing first-line regimen is still widely used in most resource constrained countries including Zimbabwe. There is a paucity of studies exploring the effect of stavudine-containing antiretroviral therapy on plasma lactate levels in the Zimbabwean population. Thus, the present study set to investigate the impact of a stavudine-containing ARV first-line regimen on plasma lactate levels and to ascertain other risk factors associated with hyperlactataemia in these patients.

Methodology

In this prospective cohort study, 180 consenting HIV-positive but ART naive adult patients who were about to be initiated on STALANEV(stavudine, lamivudine and nevirapine) at Beatrice Road Infectious Diseases Hospital (BRIDH) and Wilkins Infectious Diseases Hospital (WIDH) opportunistic infections (OI) clinics in Harare, Zimbabwe were enrolled into the study. Ninety eligible participants were enrolled consecutively from each centre over a period of two weeks. Hypertensive patients and those with a self reported history of hypoglycaemia, anti tuberculous treatment or any other long term drug therapy were excluded as were those with baseline hyperlactatemia.

Three millilitres whole blood samples were collected with minimum venostasis into a fluoride oxalate vacutainer tube from each eligible participant. Plasma lactate levels were determined prior to ART initiation (baseline) and for the next four months at 2 monthly intervals. Blood samples were collected after each participant had rested for at least 20 minutes and blood samples from BRIDH were immediately placed on an ice bath for transportation to WIDH laboratory where they were centrifuged to harvest plasma within 30 minutes of collection.

Plasma lactate analysis was performed on the Selectra E analyzer using an ABX Pentra Lactic Acid commercial kit supplied by HORIBA ABX (United Kingdom). In this assay L-lactate is metabolised to pyruvate in the presence of lactate oxidase triggering the release of hydrogen peroxide, which reacts with 4-aminoantipyrine and N-ethyl-N-sulfopropyl-m-anisidine (ESPAS) in the presence of peroxidase to form a coloured complex, quinoneimine. The intensity of the colour formed is measured at 505nm and is proportional to the amount of lactate present in the sample. All lactate assays were processed immediately after separation of plasma.

Ethical approval was granted by the University of Zimbabwe's College of Health Sciences and Parirenyatwa Hospital Joint Research Ethics Committee. Permission to access patients from BRIDH and WIDH OI clinics and to perform lactate assays was granted by the City of Harare Directorate of Health Ethics Committee. All participants gave written informed consent and completed a questionnaire eliciting demographic and general health status. Baseline CD_4 counts were accessed from eligible participants' clinic records.

Results

The participants' ages ranged from 20-68 years with a median of 36.6 years (sd 9.8) and they were all successfully followed up to the conclusion of the study. The 180 participants comprised 114 females (63.3%). Baseline CD4 counts ranged from 11-205cells/μL (median 148) and 97.7% (n = 176) of the participants had CD4 counts less than 200 cells/μl. The majority of

the participants 68.9% (n=154) were in WHO stage 3 or HIV disease and 12.9% (n=23) were in stage 2.

Figure 1: Plasma lactate levels at baseline, after 2months and after 4months follow-up. (n=180 for each timeline

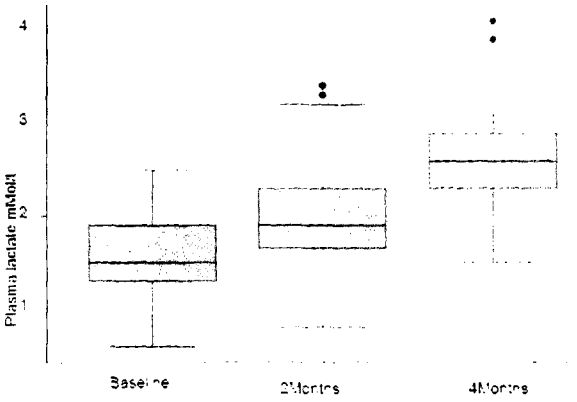

Figure I, summarises plasma lactate levels at each of the three stages when blood samples were drawn. Baseline plasma lactate levels ranged from 0.6 2.5 mmol/L with a mean of 1.57mmol/L (sd 0.43). After 2months on STALANEV the mean plasma lactate was 1.99mmol/L (sd 0.49) and 2.65mmol/L (sd 0.55) after 4months on treatment. There was a statistically significant increase in plasma lactate from baseline to 2months on STALANEV and from 2months to 4months on therapy ($p<0.001$).

The proportion of participants with hyperlactatemia increased statistically significantly ($p<0.001$) from 2months to 4months on treatment with STALANEV. After two months on STALANEV, 13.9% (n=25) of the participants had hyperlactatemia defined as a plasma lactate above 2.5mmol/L. The incidence of participants with hyperlactatemia increased to 54% (n =98) at the conclusion of the study after follow up and 7.8% (n=14) had developed mild lactic acidosis defined by plasma lactate levels above 3.5mmol/L. Of these 14 participants, only 1.7% (n=3) developed moderate lactic acidosis with plasma lactate levels above 3.9mmol/L. There was no statistically significant difference in the incidence rates between males (53% n=35) and females (55% n=63) ($p>0.05$).

Univariate linear regression indicated that a low CD4 count was a statistically significant determinant of the risk of developing hyperlactatemia ($p<0.001$) whereas the HIV/AIDS disease stages 3 and 4 weakly determined hyperlactatemia risk ($p=0.043$). Neither age nor gender were risk factors of developing hyperlactatemia in the present study.

Discussion

This study confirms a high incidence of hyperlactatemia in patients treated with STALANEV (a stavudine containing regimen). The finding is agreement with other studies done in Botswana[4], South Africa[2,5] and Uganda [6] which reported similar findings. Management of symptomatic lactic acid alterations involves treatment interruption and supportive care or where possible, switching to an alternative formulary.[7] The natural history of hyperlactataemia is still unknown, and it is uncertain whether asymptomatic patients with increased lactate concentrations are at increased risk of developing lactic acidosis.

Mild-to-moderate, asymptomatic hyperlactataemia has been frequently reported in human immunodeficiency virus (HIV)-infected patients treated with nucleoside reverse transcriptase inhibitors, with an estimated prevalence between 15% and 35% in Caucasian populations.[8] Prevalence rates have been reported to be higher in Black women[9]- a finding confirmed by the present study. Symptomatic, severe hyperlactataemia and lactic acidosis on the other hand, are less common, with an incidence ranging from 1.7 to 25.2 cases per 1000 person-years of antiretroviral treatment, but are associated with a remarkable mortality rate, which varies from 30% to 60%.[10-11] In the present study, only 1.7% (n=3) participants developed moderate hyperlactatemia and were referred for clinical management.

There was a 20% and a 59% rise in mean plasma lactate levels from baseline to two months and from baseline to four months on treatment respectively. It is likely that severe lactic acidosis would have been observed if the participants had been followed up for a longer duration. Stavudine contained in the STALANEV regimen has been previously reported as the precipitating agent due mitochondrial toxicity effects.[4-6]

In the present study, the CD4 count and HIV/AIDS disease stage were significant predictors of the risk developing hyperlactatemia. Age and gender were not predictive of developing hyperlactatemia. This finding was at variance with literature which reports females, a higher body mass index and advanced age as risk factors of developing hyperlactatemia.[4-6] However in the present study mean plasma lactate levels after 4months follow up were higher in female participants with a mean of 2.67 mmol/L (sd 0.54) compared to that for male participants with a mean of 2.61 (sd 0.57). The difference was however not statistically significant ($p>0.05$). Though not demonstrated in the present study, the mechanism for the sex difference in rates of hyperlactatemia rates is still not clearly elucidated. However, plausible explanations include possible sex-linked mitochondrial genetic differences which could increase females' susceptibility or the predisposition of obese women to hepatic steatosis, which may increase their risk.[12]

In resource constrained settings, challenges in the diagnosis and management of symptomatic hyperlactatemia remain because estimation of plasma lactate concentration is largely unavailable routinely. When available in private facilities, the cost is often beyond the reach of many. Clinical diagnosis of lactic acidosis is challenging because of nonspecific symptoms and may be confused for symptoms of malaria or gastroenteritis.

The weaknesses of the present study however include the limited follow up period which made it difficult to determine medium to long term adverse reactions if any. It could also have been ideal to compare the incidence rates of hyperlactatemia between groups on first line regimens without stavudine. Finally, the data gathered for risk factors determination could also have included factors such as the body mass index.

Conclusions

Although Stavudine is no longer recommended as a first line treatment agent, its use has continued in resource constrained settings because of relatively lower production costs. Policy makers thus need to prioritise availability of alternative regimens if mortality rates due metabolic complications are to be reduced. These toxicities related to antiretroviral therapy also make long-term compliance to therapy difficult for patients.

However, because the current formulary restrictions appear unlikely to change soon, health providers in resource-poor countries must familiarise with the common adverse events associated with long term anti viral therapy and must understand how to manage them with what is locally available.

Alternatively, routine plasma lactate assays could be introduced at affordable cost in state institutions to allow routine scheduled monitoring of patients. This could be an affordable option for resource constrained settings since point-of-care devices which provide simple, accurate measurements of lactic acid levels at relatively low cost, are now available. Use of these devices would greatly improve clinical decision-making.

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