Study of Lactic Acidosis Induced by ART Drugs

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ABSTRACT
The aim of the study was to compare the serum lactate levels and the incidence of lactic acidosis in either gender of HIV seropositive individuals on ART with stavudine or zidovudine combination drugs and to evaluate the association between duration of Antiretroviral therapy and changes in the level of lactic acid. This is a hospital based prospective study. After obtaining informed consent, blood samples were collected from the patients and lactic acid levels were measured using lactate assay kit and the association between the duration of antiretroviral therapy and changes in lactate level were evaluated. The collected data were analyzed using the Statistical software namely SAS 9.0, SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0. Among 70 patients included in the study, 34 (48.6%) were males and 36 (51.4%) were females. In this study shows that, incidence of lactic acidosis is higher in female gender. Of the total patients 46 (65.7%) received d4T regimen and 24 (34.3%) received AZT regimen. A higher S.Lactate level was found to be in patients receiving stavudine than in zidovudine therapy. In this study, S.Lactate level was found to be high in the group receiving ART since 24 months followed by 18-24 months, 12-18 months, 6-12 months, and a minimum level in 6 months. This study suggests the increased risk of lactic acidosis with longer duration of NRTIs therapy. This study confirms that, a higher incidence of lactic acidosis in female gender and the risk of this complication increases with long term use of NRTIs.

Keywords: ART, HIV infection, lactic acidosis, NRTIs

INTRODUCTION
Antiretroviral therapy has led to significant decrease in the mortality and morbidity associated with human immunodeficiency virus infection. Currently used main classes of antiretroviral agents are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors. NRTIs can be used with other NRTIs, or in combination with NNRTI or protease inhibitors as a part of highly active antiretroviral therapy (HAART) [1]. NRTIs have been widely used as a part of antiretroviral therapy against HIV. However, one recently recognized serious complication of NRTIs is the development of lactic acidosis [2]. Lactic acidosis, characterized by metabolic acidosis and a blood lactate level higher than 5 mmol/L, is generally classified as either anaerobic (type A) or aerobic (type B). The common NRTIs implicated include zidovudine (AZT), stavudine (d4T) and didanosine (ddI) have been observed to be more often implicated in case of lactic acidosis than other NRTIs.

MATERIALS AND METHODS
The aim of the study was to compare the serum lactate levels and the incidence of lactic acidosis in either gender of HIV seropositive individuals on ART with stavudine or zidovudine combination drugs as well as to evaluate the association between duration of Antiretroviral therapy and changes in the level of lactic acid. This is a hospital based prospective study. After obtaining informed consent, blood samples were collected from the patients and lactic acid levels were measured using...
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**RESULTS**

(Table 1) Shows the average S. Lactate level in females to be 41.01±29.93 mg/dl and in males to be 39.68±18.06 mg/dl.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of patients</th>
<th>CD4 counts</th>
<th>Haemoglobin</th>
<th>S. Lactate(mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34</td>
<td>297.39±176.22</td>
<td>11.53±2.08</td>
<td>39.68±18.06</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>382.58±179.41</td>
<td>10.53±1.59</td>
<td>41.01±29.93</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>341.21±181.71</td>
<td>11.01±1.89</td>
<td>40.37±24.71</td>
</tr>
<tr>
<td>P value</td>
<td>0.049*</td>
<td>0.026*</td>
<td>0.823</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 and 2: Comparison of CD4 count, Haemoglobin and Serum Lactate (mg/dl) according to gender

Serum Lactate (mg/dl) based on duration of therapy: (Table 2) shows a maximum S. Lactate level of 84.33±68.35 in group V with duration of ART 24 months.

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration of therapy</th>
<th>Number of patients</th>
<th>S. Lactate (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Up to 6 months</td>
<td>4</td>
<td>31.13±12.14</td>
</tr>
<tr>
<td>II</td>
<td>6-12 months</td>
<td>18</td>
<td>36.08±18.31</td>
</tr>
<tr>
<td>III</td>
<td>12-18 months</td>
<td>33</td>
<td>39.88±21.50</td>
</tr>
<tr>
<td>IV</td>
<td>18-24 months</td>
<td>12</td>
<td>40.20±22.16</td>
</tr>
<tr>
<td>V</td>
<td>&gt;24 months</td>
<td>3</td>
<td>84.33±68.35</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>70</td>
<td>40.37±24.72</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>-</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

Figure 3: Serum Lactate (mg/dl) based on duration of therapy
DISCUSSION

The incidence rate of lactic acidosis was higher in HIV infected patients on HAART. Predisposing factors for lactic acidosis were being on stavudine containing regimen and being female. The association between these factors and the development of NRTIs induced lactic acidosis has been confirmed by other studies [3, 5, 6].

A total of 70 patients studied; with maximum of 30 patients (42.9%) were found to be in the range of 31-40 years, 20 patients (28.6%) were found to be in the range of up to 30 years, 13 patients (18.6%) in the range of 41-50 years and 7 patients (10%) in the range of above 50 years. Of these 70 patients who were reviewed, 34 patients (48.6%) were males and 36 patients (51.4%) were females. The larger number of female patients in our study shows that incidence of lactic acidosis is higher in female gender than male (Table 1).

Of these 70 patients who were reviewed, 34 patients (48.6%) were males and 36 patients (51.4%) were females. The larger number of female patients in our study shows that incidence of lactic acidosis is higher in female gender than male. In one study, Moyle et al [3] revealed that females were over represented among 9 patients with severe lactatemia, and, in another study with a review of 40 case patients, Megarbane et al [4] stated male to female ratio of 1.18: 1, which represents a higher rate of lactic acidosis among females when one take into account of higher prevalence of HIV infection in male.

In the present study, a maximum S. Lactate level of 84.33±68.35 mg/dl was found to be in the group receiving ART since 24 months, 40.20±22.16 mg/dl in group receiving ART in the range of 18-24 months, 39.88±21.50 mg/dl in the range of 12-18 months, 36.08±18.31 mg/dl in the range of 6-12 months, and 31.13±12.14 in the group receiving ART since 6 months. Our study suggests that, increased risk of lactic acidosis with longer NRTI exposure (Table 2).

CONCLUSION

In conclusion we have found that two main risk factors for lactic acidosis: female genderand cumulative NRTI exposure. Even though severe hyperlactatemia and lactic acidosis are rare serious complications of antiretroviral therapy, it is a major co-morbid event. An important observation is that in NRTI induced lactic acidosis can develop at any stage of HIV disease. Several issues concerning nucleoside associated lactic acidosis remain unsolved especially with regard to prevention and treatment.

REFERENCES


Anilasree B P et.al, JPRCP 2014; 4(2)