Electrolyte imbalance and sleep problems during anti-retroviral therapy: An under-recognized problem

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ABSTRACT

Human immunodeficiency virus (HIV) infection, and the anti-retroviral therapy (ART) associated complications necessitate that the medical care system keeps evolving for proper management of this group of patients. Electrolyte imbalance and sleep problems are common in patients on ART. Both of these conditions are associated with increased morbidity (such as acute kidney injury, chronic kidney disease, low CD4 count, non-adherence and depression) and mortality. Therefore, screening for both sleep problems and electrolytes imbalance may help to decrease the risk of complications in patients on ART.

Keywords: Mortality; Water-Electrolyte Imbalance; Anti-Retroviral Agents; AIDS Serodiagnosis.

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Received: March 30, 2017;
Accepted: May 12, 2017.

DOI: 10.5935/1984-0063.20170011
INTRODUCTION

Human immunodeficiency virus (HIV) infection and the ensuing acquired immune deficiency syndrome (AIDS) is a global pandemic, and 78 million people have become infected with HIV since the start of the epidemic. Although HIV-related mortality has seen decline of approximately 45% since 2005, mortality is still staggering with 1.1 million deaths in 2015. Expansion of accessibility to antiretroviral treatment (ART) has considerably reduced the incidence of new HIV infections, AIDS mortality and its related co-morbidities. However, ART related complications, associated mortality and non-adherence to therapy are major challenges that necessitate a steadfast and evolving healthcare management. Therefore, persistent systematic exploration for factors, which may be prospective clinical markers for management of ART related major complications and that minimize associated mortality and non-adherence are needed.

ART is the cornerstone of the ever-evolving clinical management scheme of patients with HIV infection and or AIDS. ART regimens include different combinations of drugs from various classes of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors and integrase inhibitors. The use of ART has presented new challenges to both patients and health care providers. Proper management of adverse effects and identification of predictors of non-adherence and mortality need continuous evolution.

The innovative clinical use of mortality predictors may help reduce mortality and manage morbidity. Both HIV infection and ART lead to adverse physiological changes, which are predisposing factors for sleep problems and electrolyte complications. This brief review summarizes the evidence of ART-related electrolyte imbalance and sleep problems. Further, previous evidence of supporting a relationship between these two conditions and mortality or predictors of mortality in patients on ART is streamlined in a model (Figure 1). Additionally, it is proposed that screening for sleep problems and electrolyte imbalance may help to reduce mortality and morbidity in patients on ART.

ELECTROLYTE IMBALANCE AND ANTI-RETROVIRAL THERAPY

Renal complication such as acute kidney injury (AKI) and chronic kidney disease (CKD) have been reported to occur in patients on ART. Moreover, patients on ART may develop a variety of electrolyte disturbances including, hyponatremia, hypokalemia, hypocalemia and others. These electrolyte disturbances are related to the type of drug used. Table 1 shows a list of drugs used in ART and the electrolyte disturbances usually associated with them. Electrolyte imbalance represents a major problem in patients receiving ART.

African women on ART regimens including nevirapine or efavirenz plus lamivudine with either stavudine or zidovudine have been reported to develop electrolyte imbalances namely hyponatremia and hypochloremia. Didanosine is associated with several electrolyte imbalances including hypomagnesemia, and hypocalemia. Didanosine, Tenofovir use have been reported to be associated with AKI, severe hypokalemia and hypophosphatemia. The combination of protease inhibitors (i.e. ritonavir with tenofovir) has been shown to increase susceptibility to renal toxicity. Hypophosphatemia was found in Zambian adults on ART regimens of efavirenz or nevirapine in combination with lamivudine with either zidovudine or stavudine.

Sleep problems and anti-retroviral therapy

HIV infected patients have a high prevalence of insomnia and complaints of daytime sleepiness. Sleep-disordered breathing was high in patients using ART. Increased neck circumference, and obesity are potential risk factors for Obstructive sleep apnea among HIV patients on ART. The investigations into potential physiologic causes of insomnia in ART are marred by inconsistencies. Of the psychosocial factors, stress associated with HIV infection may be implicated in onset of insomnia. Moreover, depression shares a direct relationship with insomnia, which may further explain stabilization of insomnia in these patients with treatment.
Sleep problems, electrolyte imbalance and predictors of mortality

Figure 1 presents a schematic representation of the proposed relationship between sleep problems, electrolyte imbalance, and major predictors of mortality i.e. depression, non-adherence of ART, low CD4 count, AKI and CKD in patients on Anti-retroviral therapy (ART).

The relationship model is based on the epidemiological studies in different demographics across the world. Hyponatremia and hypochloremia in patients on ART regimens including nevirapine or efavirenz plus lamivudine with either stavudine or zidovudine increased the risk of mortality by 7.8 times in African women. Baseline serum phosphate was found to be an independent predictor of mortality in Africans on ART. Hypomagnesemia is very common in AIDS patients. It is a major risk factor for AKI, sepsis, non-recovery of renal function and consequent mortality.

Sleep disturbances as well as poor overall sleep quality in women on ART therapy are associated with low CD4 count, which is a strong predictor of AIDS related mortality. Insomniac HIV-infected persons have a decreased daily activity. Insomnia is associated with an increased waist circumference and depression. Women with greater sleep disturbance were associated with depression symptoms and poor adherence to their ART regimen.

This suggests that screening for sleep disturbance may help to identify prospective non-adherents. Poor sleep quality was associated with non-adherence and depression, which is again a predictor of non-adherence in American patients on ART. Moreover, it has been shown that individuals with insomnia and bad dream complaints are poor adherents of ART. Adherence to ART was associated with CD4 count in the sub-Saharan African country of Togo. Screening for both sleep problem and electrolyte imbalance especially hyponatremia, hypochloremia, hypomagnesemia and hypophosphatemia may help decrease risks of complications-associated death in antiretroviral therapy. The model linking sleep problem/electrolyte imbalance and mortality and non-adherence in patients on ART should be studied further to help in the management of HIV/AIDS patients.

Compliance with Ethical Standards
Funding Statement

No funding has been reported for this study.

Disclosure of potential conflicts of interest

The authors have read the journal’s policy and have the following potential conflicts: S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. This does not alter the authors’ adherence to all the journal policies.

All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

Table 2. Sleep and associated problems reported for some common drugs used in antiretroviral therapy.

<table>
<thead>
<tr>
<th>Sleep and associated problems</th>
<th>Drugs used in anti-retroviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbances</td>
<td>Efavirenz, Tenofovir, Lamivudine</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Lamivudine, Zidovudine, Rilpivirine, Anazanavir, Cobicistat, Dolutegravir, Raltegravir</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>Efavirenz, Cobicistat, Dolutegravir</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Cobicistat</td>
</tr>
<tr>
<td>Depression</td>
<td>Efavirenz, Rilpivirine, Tenofovir, Cobicistat</td>
</tr>
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Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable for this study.

REFERENCES


Sleep Sci. 2017;10(2):64-67