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Original article

The role of nucleoside reverse transcriptase inhibitors usage in the incidence of hyperlactatemia and lactic acidosis in HIV/AIDS patients

Gordana Dragovic [a,*], Djordje Jevtovic [b]

[a] Institute of Pharmacology, Clinical Pharmacology and Toxicology, Dr Subotica 1/III, School of Medicine, University of Belgrade, Belgrade, Serbia
[b] Institute of Infective and Tropical Disease "Dr Kosta Todorovic", Bulevar JNA 16, School of Medicine, University of Belgrade, Belgrade, Serbia

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ABSTRACT

Hyperlactatemia and lactic acidosis (LA) are among the most dangerous and life-threatening side effect that occurs during therapy with some nucleoside reverse transcriptase inhibitors (NRTIs), mainly didanosine (ddI) and stavudine (d4T), also known as d-drugs. Therefore, we performed a prospective, follow-up study and aimed to examine the incidence rates (IR) and rate ratios (RR) of hyperlactatemia and LA for each NRTI. Three hundred and ninety-six HIV-patients were included in final analysis comprising 783.8 person-years of follow-up. Between 1st January 2000 and 1st January 2008, 19 cases of hyperlactatemia and 15 cases of LA were recorded. Between regimens with the significant impact for developing hyperlactatemia and LA the lowest IR was for didanosine (IR = 2.87 per 100 person-years, 95%CI = 0.45–9.25 and IR = 4.31 per 100 person-years, 95%CI = 1.07–13.91, respectively), and the highest for didanosine + stavudine (IR = 10.17 per 100 person-years, 95%CI = 1.02–19.76 and IR = 7.39 per 100 person-years, 95%CI = 1.02–13.05, respectively). Compared to didanosine alone the RR of hyperlactatemia was 2.67 (95%CI = 1.11–12.52) for stavudine, and 4.06 (95%CI = 1.31–15.48) for didanosine + stavudine. The RR of LA was 3.12 (95%CI = 1.13–10.65) for stavudine, and 5.13 (95%CI = 1.54–13.37) for didanosine + stavudine in comparison with didanosine alone. Other risk factors for AP were CD4 cell count less than 200 cells/mm^3 and female sex. Our results suggest that the use of stavudine alone or in combination with didanosine should not be used as first-line therapy, especially in patients with CD4 cell count less than 200 cells/mm^3 and females if other treatment options are available.

1. Introduction

Although antiretroviral therapy (ART) has led to a dramatic decline of human immunodeficiency virus (HIV) related morbidity and mortality, clinically important drug toxicities can limit the use of these agents. Hyperlactatemia and lactic acidosis are among the most dangerous and life-threatening side effect that occurs during therapy with some nucleoside reverse transcriptase inhibitors (NRTIs) [1], mainly didanosine (ddI) and stavudine (d4T), also known as d-drugs [1–3]. Although the European AIDS Clinical Society (EACS), International AIDS Society-USA panel and the British HIV Association guidelines for HIV therapy no longer recommend these d-drugs as part of a first-line regimen due to these toxicities [4–6], there are still low and low-middle income settings in the world in which ddI and d4T are still prescribed in the first-line therapy [7].

HIV/AIDS Centre in Belgrade, Serbia, is a low-middle income setting, which had limited or no access to the newer NRTIs with lower toxicity rates on the time when the study was conducted and therefore, necessarily used d-drugs in a routine daily practice [8].

The aim of this study was to investigate the incidence of hyperlactatemia and lactic acidosis associated with nucleoside reverse transcriptase inhibitors usage in HIV/AIDS cohort of antiretroviral-naïve patients commencing HAART in Belgrade, Serbia.

2. Materials and methods

2.1. Patients

Patients were attendees at the out-patients clinic at the HIV/AIDS Centre, Infectious and Tropical Diseases Clinic, "Kosta Todorovic", Clinical Centre of Serbia, Belgrade. During the study period this centre was the sole provider of antiretroviral therapy in Serbia, caring for over 1200 patients with HIV infection.

For this study, we included all HIV/AIDS patients who started antiretroviral therapy between 1st January 2000 and 1st January 2008. During the study period patients were followed from the date of starting antiretroviral treatment until the date of stopping at least one of the antiretrovirals included in the NRTI backbone of

* Corresponding author. Tel.: +381 65 2721 180; fax: +381 11 3643 397.
E-mail address: gozza@beotel.net (G. Dragovic).

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the HAART regimen, the date they were last seen at their clinic, or the 1st January 2008, whichever occurred first. All immunological, virological, hematological and biochemical data are collected every 3 months from all patients taking therapy, together with information on antiretroviral and concomitant medication. All tests, results, procedures, drug history and clinical events data are routinely collected and maintained on our local database prospectively together with other routinely collected information.

We described the characteristics of the patients focussing on the NRTI backbone prescribed and particularly the use of d4T and ddI. We also collected information on gender, ethnicity, age, risk group, Hepatitis B virus (HBV) status, Hepatitis C virus (HCV) status, CD4 count at starting HAART and HIV plasma viral load and other laboratory measurements and any new clinical diagnoses. Pregnant women were not included in the study.

All patients included in this study were treated with one or more NRTIs in combination with protease inhibitors (PI), or non-nucleoside reverse transcriptase inhibitors (non-NRTIs). NRTIs included zidovudine, lamivudine, abacavir and d-drugs didanosine (ddI) and stavudine (d4T), since tenofovir and emtricitabine have not been registered in Serbia. PIs included nelfinavir, indinavir (IDV), saquinavir (SQV), ritonavir (RTV) and lopinavir/RTV, and NNRTIs efavirenz and nevirapine.

All patients receiving NRTIs were categorized into six groups. Each group of patients was treated with at least one NRTI-containing regimens: zidovudine (250 mg BID), lamivudine (150 mg BID, without dietary restrictions), didanosine (body weight $\geq$ 60 kg 400 mg QD; body weight $<$ 60 kg 250 mg QD), stavudine (body weight $\geq$ 60 kg 40 mg BID; body weight $<$ 60 kg 30 mg BID), abacavir (300 mg BID) and the combination didanosine + stavudine. Other NRTI backbones were AZT + 3TC, ddI + 3TC and ABC + 3TC.

For this study, the main outcome was the first episode of hyperlactatemia or lactic acidosis for each case. All study participants were HIV-1-infected adults, older than 18 years. In order to diagnose hyperlactatemia and lactic acidosis, patients were counseled how to recognize the early symptoms. Any appearance of symptoms which may be attributed to the hyperlactatemia and/or lactic acidosis, such as fatigue, nausea and vomiting were the reason for testing patients' blood sample for the lactate levels and acid-base status. Patients with hyperlactatemia were included if they had at least two consecutive readings of blood lactate greater than 5 mmol/l (450 mg/l) regardless of their acid-base status. Lactic acidosis was defined as arterial blood pH less than 7.35, blood bicarbonate less than 20 mmol/l and blood lactate levels above the upper limit of the reference range in the relevant centre. Samples for lactate levels were collected at rest in fluoride tubes (to prevent further lactate production) and processed on the same day. The episode date for each case was the date when the case definition was met (i.e. the confirmatory reading greater than 5 mmol/l for hyperlactatemia or the date of the first low blood pH and bicarbonate for lactic acidosis). Clinical data were not included in the case definition since the symptoms associated with lactic acidosis and hyperlactatemia are mainly nonspecific and frequently seen in HIV-1-infected patients taking ART [8]. Other causes for hyperlactatemia and lactic acidosis such as obesity, female sex, pregnancy and drug usage of ribavirin and hydroxyurea were excluded from the analysis.

Consent for participation was obtained from all patients, and the study was approved by the Clinical Centre of Serbia Ethics Committee, Belgrade, Serbia.

2.2. Statistical analysis

Poisson regression analysis was used to assess the relative rate of developing either hyperlactatemia or lactic acidosis for each NRTI regimen. Incidence rates (IR) for each of the NRTI-containing regimens were calculated by using the number of cases of hyperlactatemia or lactic acidosis associated with a particular regimen as the numerator and the total amount of person-time accumulated on the corresponding regimen as the denominator. If acute hyperlactatemia or lactic acidosis developed, only time to development of hyperlactatemia or lactic acidosis was included. The crude rate ratios (RR) with 95% confidence intervals (CI) of development of hyperlactatemia or lactic acidosis for each NRTI regimen were calculated. Only variates with a $P < 0.05$ were retained in the final model. Univariate and stepwise multivariate logistic regression models were used to asses the odds ratios (OR) of developing hyperlactatemia or lactic acidosis for these variables: age, gender, CD4 cell count, concomitant PI or non-NRTI drug use and duration of prior NRTI use.

3. Results

During the study period there were 396 patients treated with one or more NRTIs in combination with PI or non-NRTIs, comprising 783.8 person-years of follow-up on NRTIs. In this cohort, there were 234 male (59.1%) and 162 female (40.9%) patients, all Caucasians. Median (interquartile range [IQR]) age was 37 years (31, 45). When starting HAART patients had advanced disease; 324 (81.8%) had a prior AIDS diagnosis and the median (IQR) CD4 cell count at baseline was 112 cells/mm^3 (61, 197) and the median basal viral load was 4.8 $\log_{10}$ copies/mL (range: 3.25–5.98) (Table 1).

During the study period there were 19 cases of hyperlactatemia (none of the patients died) and 15 cases of lactic acidosis (five patients died). The lowest IR for hyperlactatemia and LA was for didanosine (IR = 2.87 per 100 person-years, 95%CI = 0.45–9.25 and IR = 4.31 per 100 person-years, 95%CI = 1.07–13.91, respectively), and the highest for didanosine + stavudine (IR = 10.17, 95%CI = 1.02–19.76 and IR = 7.39 per 100 person-years, 95%CI = 1.02–13.05, respectively). The number of cases of hyperlactatemia and lactic acidosis, person-years and incidence rates (cases per 100 person-years) among each of the NRTI-containing regimens are presented in Tables 2 and 3.

For stavudine, the adjusted RR of developing hyperlactatemia and lactic acidosis was 2.67 (95%CI = 1.11–12.52) and 3.12 (95%CI = 1.13–10.65), respectively, in comparison with didanosine alone. While for combination of two nucleoside analogs didanosine + stavudine, the adjusted RR of developing hyperlactatemia and lactic acidosis was 4.06 (95%CI = 1.31–15.48) and 5.13

Table 1
Patient characteristics at starting antiretroviral therapy.

Value	
Risk for HIV transmission	
Homosexual	167 (42.2%)
Heterosexual	136 (34.3%)
IDU	80 (20.2%)
Other	13 (3.3%)
Gender	
Male	234 (59.1%)
Female	162 (40.9%)
Age Median (IQR)	37 (31, 45)
CDC category	
A2	32 (8.1%)
A3	30 (7.6%)
B2	40 (10.1%)
B3	96 (24.2%)
C2	18 (4.5%)
C3	180 (45.5%)
Pre-treatment CD4 count (cells/mm^3)	
Median (IQR)	112 (61, 197)
Pre-treatment viral load ($\log_{10}$ copies/ml)	
Median (IQR)	4.8 (3.25–5.98)