

Symptomatic hyperlactatemia in an HIV-positive patient: a case report and discussion

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Abstract

PROLONGED EXPOSURE TO HIGHLY ACTIVE antiretroviral therapy may be associated with adverse effects related to mitochondrial toxicity, such as hyperlactatemia. We describe a case of symptomatic hyperlactatemia in an HIV-positive patient to illustrate the subtle clinical symptoms and abnormal laboratory test results associated with this condition. We also review the pathophysiology, prevalence, spectrum and management of disturbances in lactate homeostasis induced by nucleoside reverse transcriptase inhibitors.

Case

A 41-year-old HIV-positive man began therapy with didanosine, stavudine and nevirapine 6 months after the failure of his initial regimen of zidovudine, lamivudine and nelfinavir. After 4 weeks of treatment, his viral load had decreased, from 28 450 copies/mL (4.45 log) to 126 copies/mL (2.10 log), and he appeared to be tolerating the new regimen well. Four weeks later he began experiencing nausea and vomiting, usually after his morning dose of didanosine. Over the next 2 months the nausea and vomiting persisted, and diffuse, low-grade abdominal pain developed. The patient remained afebrile and denied headaches, diarrhea, light-headedness or weakness. Findings on abdominal examination were unremarkable. The symptoms did not respond to treatment with either dimenhydrinate or prochlorperazine.

Blood work done 5 months after the initiation of this second regimen revealed the following: anion gap 17 (normally 8–16) mmol/L, lactate 3.7 (normally 0.5–2.3) mmol/L, aspartate aminotransferase 76 (normally 7–40) U/L and alanine aminotransferase 67 (normally 10–45) U/L; the levels of carbon dioxide, alkaline phosphatase and amylase were within normal limits. The following week the lactate level was 6.1 mmol/L, the carbon dioxide level was 21 (normally 22–30) mmol/L, and the anion gap measured 20 mmol/L. Subsequent rebound in viral load led to the discontinuation of the highly active antiretroviral therapy (HAART), and 4 days later the patient reported improvements in his symptoms. The lactate level the following month measured 2.0 mmol/L, and liver enzyme levels were within normal limits.

The patient has since started HAART with zidovudine, abacavir and lopinavir–ritonavir and remains asymptomatic.

His liver enzyme levels, anion gap and carbon dioxide level have remained within normal limits 12 months after initiating the new regimen; measurement of the serum lactate level has not been repeated, since the patient has been clinically well and other laboratory indices have remained stable.

Comments

Our patient's symptoms, the persistently elevated serum lactate level, the increasing anion gap and the decreasing carbon dioxide level were all felt to be consistent with hyperlactatemia secondary to the didanosine or stavudine treatment, or to the combination of the 2 NRTIs, for several reasons. There were no signs of chronic liver disease (tests for hepatitis B surface antigen and hepatitis C antibody were both negative), and there was no evidence of intercurrent illness. Also, the patient denied excessive alcohol intake during this period, and he was taking no other medication reported to cause elevated serum lactate levels. Furthermore, the hyperlactatemia was unlikely related to exercise, since the serum lactate level was measured in a blood sample taken after 15 minutes of rest on each occasion. Finally, the patient's symptoms resolved and his lactate level returned to within normal limits after discontinuation of HAART.

The advent of HAART has reduced morbidity and mortality associated with HIV infection by about 50%.^{1,2} However, the risk of adverse effects related to mitochondrial toxicity has emerged as a significant concern with prolonged antiretroviral exposure.^{3,4} Hyperlactatemia attributable to nucleoside analogue reverse transcriptase inhibitors (NRTIs) is an example of such an adverse effect. Previously reported as isolated cases of type B lactic acidosis with hepatic failure,^{5,6} hyperlactatemia characterized by mild to moderate increases in blood lactate levels in the absence of acidosis has been reported in 4%–36% of patients receiving HAART.^{7–14} Although most episodes appear to be asymptomatic, symptomatic cases have also been reported.^{15–17}

A variety of NRTIs, including stavudine, zidovudine and didanosine, have been associated with hyperlactatemia because of their potential for mitochondrial toxic effects.^{3–6,15–17} Specifically, the pharmacologically active triphosphate moieties of NRTIs act as substrates for human mitochondrial DNA polymerase gamma, thereby having the potential for incorporation into mitochondrial DNA (mtDNA). As well, mitochondrial exonuclease is inefficient at removing the

nucleoside triphosphates.^{18,19} The combination of nucleoside triphosphate incorporation and inadequate removal disrupts mtDNA synthesis and results in the arresting of mtDNA-encoded protein synthesis. Eventually, a disruption of oxidative phosphorylation ensues, and lactate accumulates.⁴ HIV-positive patients with NRTI-induced hyperlactatemia have been found to have mtDNA levels that are significantly lower than those of HIV-negative controls and of HIV-positive patients who have never taken antiretroviral therapy.²⁰ This observation lends credence to the aforementioned experimental observations. *In vitro*, zalcitabine, didanosine and stavudine are the most potent inhibitors of mtDNA synthesis.²¹⁻²³ Although alterations in lactate clearance do not appear to be important in the pathogenesis of this adverse effect, mitochondrial dysfunction in hepatocytes may decrease hepatic lactate clearance, which thereby would result in a slow normalization of lactate levels following the discontinuation of NRTI therapy.^{15,24}

Clinically, mitochondrial toxicity pertaining to serum lactate imbalance manifests in 1 of 3 forms, the most severe of which is a syndrome of fulminant lactic acidosis associated with gastrointestinal complaints and respiratory distress. Fortunately, this variant is uncommon, with an estimated incidence rate of 0.85–8.3 cases per 1000 person-years.^{11,25-27} Although reports of lactic acidosis consistently feature stavudine as a component of the causative antiretroviral regimen, there is insufficient evidence at present to quantify the risk of lactic acidosis among the various NRTIs. In contrast to lactic acidosis, an asymptomatic, mild hyperlactatemia that may be chronic or intermittent in nature represents the most common and least severe presentation of NRTI-induced disruptions in lactate homeostasis. In a prospective, longitudinal study involving 349 patients receiving antiretroviral therapy, the mean lactate level did not exceed 3.5 mmol/L in the majority of patients with elevated lactate levels over an 18-month period.¹¹ Similar results were obtained in a 4-week cross-sectional study involving 880 patients receiving antiretroviral therapy: the majority of cases of documented hyperlactatemia were mild (1.1–2 times the upper limit of normal).¹³ In both studies, the lactate levels were marginally but significantly higher in patients receiving stavudine-based regimens than in those receiving zidovudine-based regimens. Adjustment for duration of total NRTI exposure or duration of past zidovudine use in stavudine users did not alter this association, which suggests that the increased risk ascribed to stavudine was not confounded by a longer history of NRTI exposure.

Symptomatic hyperlactatemia in the absence of acidosis lies between asymptomatic hyperlactatemia and lactic acidosis in terms of severity on the spectrum of NRTI-induced serum lactate disturbances. Features of this syndrome include unexplained abdominal pain, nausea, vom-

iting, weight loss and fatigue. Symptoms may also be accompanied by mild transaminitis and hepatic steatosis. As well, cases of stavudine-associated rapidly ascending neuromuscular weakness and respiratory failure mimicking Guillain-Barré syndrome have been recently reported in the context of hyperlactatemia.²⁸ Although hyperlactatemia has been linked with lipoatrophy, peripheral neuropathy and osteopenia, it is unclear whether these associations are causative or whether they reflect widespread mitochondrial toxicity.^{13,29-31}

The estimated incidence and prevalence of symptomatic hyperlactatemia have been reported as 10.8–14.8 cases per 1000 person-years and 0.8% per year, respectively.^{15,16,27} However, the incidence and prevalence may vary depending on the number and choice of NRTIs present in an antiretroviral regimen. In a longitudinal cohort study involving 2144 patients receiving NRTI therapy, the risk of symptomatic hyperlactatemia increased more than 2-fold for each additional NRTI used in a given regimen.³² Different combinations of NRTIs were also associated with different rates of symptomatic hyperlactatemia. The incidence was highest with the combination of stavudine and didanosine (59.4 cases per 1000 person-years) and lowest with the combination of zidovudine and lamivudine (3 cases per 1000 person-years). In a separate study the incidence of symptomatic hyperlactatemia was calculated as 25.6 cases per 1000 person-years for any regimen containing stavudine, as compared with 1.9 cases per 1000 person-years for regimens without stavudine.³³ Similarly, the prevalence of symptomatic hyperlactatemia increases to 1.2% per year if only patients treated with a stavudine-based regimen are considered.¹⁶

Thus, the use of stavudine as part of antiretroviral regimens may be associated with an increased risk of symptomatic hyperlactatemia relative to other NRTIs. This association corroborates *in vitro* data identifying stavudine as a potent inhibitor of mtDNA synthesis and is supported by anecdotal reports of clinical improvement and normalization of lactate levels when stavudine is replaced by an NRTI with a lower propensity for mitochondrial toxicity (e.g., abacavir).¹⁷ However, this association should be made cautiously, since most of the data collected thus far are from uncontrolled observational studies, and cases of lactic acidosis and hyperlactatemia have been reported with other NRTIs.^{5,6,34}

Routine monitoring of serum lactate levels does not appear to be warranted. Although our patient had clinical manifestations of hyperlactatemia, experience with this adverse effect thus far suggests that a pattern of chronic, mild, asymptomatic hyperlactatemia with lactate levels below 3.5 mmol/L is more typical.¹¹ The significance of chronically elevated levels of serum lactate has yet to be deter-

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) that may cause hyperlactatemia

- Didanosine
- Stavudine
- Zalcitabine
- Zidovudine

mined. Mild, asymptomatic elevations in lactate levels have not been predictive of progression to lactic acidosis,^{8,11} and a positive predictive value of only 39% for the confirmation of lactic acidemia following a single elevated value has been recently reported.³⁵ As well, it is unclear whether the cases of symptomatic hyperlactatemia reported thus far would have continued to progress to lactic acidosis had treatment continued without intervention. Given that lactic acidosis can present quite precipitously and progress in a fulminant manner and that patients can be relatively asymptomatic even with high lactate concentrations, lactate levels should be measured when patients taking antiretroviral therapy have unexplained symptoms consistent with hyperlactatemia (e.g., nausea, vomiting, abdominal pain, dyspnea, fatigue, weight loss and elevated liver enzyme levels).

Although the optimal management of patients with hyperlactatemia remains unclear, our current approach is to consider changing NRTIs for patients with lactate levels between 2 and 5 mmol/L who are symptomatic or are experiencing a concomitant fall in their serum bicarbonate level, or both. In one study, 48-week data have suggested that substitution of abacavir or zidovudine for stavudine is safe and is associated with decreases in serum lactate levels, although the size of the cohort studied was small.³⁶ Patients with chronic or intermittent asymptomatic hyperlactatemia are followed periodically for the onset of signs and symptoms of hyperlactatemia, but no imminent change in their management is usually considered in the interim. Because of the precipitous and fulminant nature of lactic acidosis, antiretroviral therapy should be interrupted in patients with lactate levels greater than 5 mmol/L. Depending on the severity of the presentation, a challenge with NRTIs associated with a lower risk of mitochondrial toxicity based on in vitro data (e.g., abacavir, tenofovir, lamivudine) may be considered.³⁷ Alternatively, regimens lacking NRTIs can be considered for patients who recover from NRTI-induced lactic acidosis. Genotypic resistance testing, in which mutations capable of conferring drug resistance are identified and patterns of drug susceptibility inferred, may also play a role in the selection of a new regimen, particularly in patients with detectable viremia before drug substitution. Our approach is in keeping with published guidelines.³⁸ However, little published data are available to guide clinicians with respect to the safety of challenging patients with NRTIs following an episode of symptomatic hyperlactatemia.

Aside from treatment discontinuation and substitution, other options for the treatment of symptomatic hyperlactatemia and lactic acidosis have not been systematically studied. Anecdotal reports exist that document the efficacy of

coenzyme Q₁₀,^{39,40} riboflavin,^{41,42} thiamine,⁴³ L-carnitine^{40,44} and vitamin B complex⁴⁴ in the treatment of lactic acidosis, although it is difficult to isolate the effect of these treatments from the impact of stopping NRTIs on the course of lactic acidosis in these cases.

Symptoms and signs suggestive of hyperlactatemia in HIV-positive patients

- Abdominal pain
- Nausea and vomiting
- Fatigue
- Dyspnea
- Weight loss
- Elevated liver enzyme levels

Conclusion

Although uncommon, symptomatic hyperlactatemia should be considered in the differential diagnosis of HIV-positive patients receiving NRTI-based HAART and presenting with vague symptoms such as fatigue, gastrointestinal complaints and dyspnea. Additional

studies are required to clarify patient risk factors for hyperlactatemia, the clinical significance of chronically elevated serum lactate values and the optimal management of NRTI-mediated hyperlactatemia.

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Competing interests: None declared.

Contributors: All of the authors were involved in researching the cause of the patient's symptoms, the literature review regarding HIV and hyperlactatemia, and the analysis and interpretation of the literature for relevance to this case. Mr. Antoniou was the principal author, and Drs. Weisdorf and Gough were involved in the critical revision of the article for important intellectual content. All authors approved the final version of the article.

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