Perspectives

Metabolic Complications in HIV Disease: Lactemia and Bone Disease

Henry Masur, MD, discussed recent information on lactemia, osteopenia, and avascular necrosis in patients with HIV disease at the International AIDS Society–USA course in New York in March.

Case History 1

A 54-year-old obese HIV-infected man presented with a 2-week history of nausea and fatigue. At presentation, he had been receiving stavudine/lamivudine/indinavir for 18 months and had a CD4+ cell count of 650/µL and viral load below detection limits. The patient had reported right hip pain for 3 months. Physical exam showed modest hepatomegaly and no range of motion abnormalities of the right hip. Laboratory tests showed mildly elevated liver function tests and a serum lactate level of 3 mmol/L, and the patient's plasma hepatitis C virus RNA assay was positive. Chest x-ray and hip x-ray were normal. Should work-up for this patient include a bone scan, magnetic resonance imaging (MRI) of the painful hip, or a computed tomographic (CT) scan of the abdomen? Should antiretroviral treatment be immediately discontinued? Should the patient's serum lactate levels be monitored?

Lactemia

Lactemia, or lactic acidemia, is defined as a venous lactate level of more than 2.5 mmol/L (>2.0-3.0 mmol/L) in the absence of abnormal arterial pH. Lactic acidosis is defined as arterial pH of less than 7.35 mmol/L with a venous lactate level of more than 2.0 mmol/L and up to 2.5 mmol/L. Most authorities classify severity of lactemia as mild for lactate levels of 2.0 to 5.0 mmol/L, moderate for levels of 5.0 to 10.0 mmol/L, and severe for levels above 10.0 mmol/L. Acidosis is rare but symptoms of lactemia are common in moderate lactemia and both acidosis and symptoms are frequent in severe cases, in which mortality rate can reach 80%.

Data from a number of sources indicate that the incidence of lactemia of any severity is about 1.5 to 2.1 cases per 100 patient-years of exposure to nucleoside reverse transcriptase inhibitors (nRTIs), including an incidence of 2.3 to 2.6 per 100 patient-years of exposure to stavudine. The incidence of moderate to severe lactemia is estimated at 0.13 to 0.8 cases per 100 patient-years of exposure to antiretroviral therapy, including an incidence of 1.2 per 100 patient-years of exposure to stavudine (Fortgang et al, A*m* J G*astro*, 1995; Gerard et al, AIDS, 2000; John et al, AIDS, 2001).

> The incidence of lactemia is approximately 1.5 to 2.1 cases per 100 patient-years of nRTI exposure

Data on the prevalence of lactemia are available from 4 cohorts. Prevalence rates of any lactemia were 21% among patients receiving nRTI therapy versus 3% in those receiving no antiretroviral therapy in a Sydney cohort of 218 patients. Rates were 8% with nRTI treatment and 1% with no therapy in a Swiss cohort of 880 patients, and 21% with nRTI therapy and 8% with no therapy in a Dutch cohort of 223 patients. Symptomatic lactemia occurred in 2.4% of patients receiving nRTIs and 0% of those receiving no therapy in the Sydney cohort, 1.3% of those receiving nRTIs and 0% of those receiving no therapy in a Perth cohort of 349 patients, and in none of the patients receiving no therapy in the Swiss cohort.

Associations of lactemia and lactic acidosis with nRTI use are established, with risk appearing to be greater with use of didanosine and stavudine, particularly the latter. Factors potentially associated with lactemia and lactic acidosis include female sex, older age, lower CD4+ cell count, underlying liver disease, duration of antiretroviral therapy, and pregnancy. With regard to pregnancy, 3 deaths due to this lactic acidosis syndrome have been reported in pregnant women receiving stavudine. Warnings have subsequently been issued by the US Food and Drug Administration (FDA) regarding use of didanosine or stavudine in pregnant patients.

The incidence of lactemia in patients receiving nRTIs increases within the first few months of treatment. Moreover, the long-term population average lactate concentrations rise over the initial 12 months of treatment (Figure 1). These findings suggest that lactate levels should be monitored with particular care over the initial 4 to 6 months of potent nRTI-containing therapy in patients who have any of the risk factors for lactic acidosis listed above, but better delineation is needed as to which patients truly benefit from regular screening, and how this screening (eg, frequency and duration) should be done.

Case History 2

A 63-year-old woman presented with a 1-month history of nausea, vomiting, and abdominal pain. She had severe acidosis (pH, 7.12; lactate level of 13.6 mmol/L), elevated liver function tests, elevated amylase and lipase levels indicative of chemical pancreatitis, and a CD4+ cell count of 192/µL. CT scan showed a fatty liver and liver biopsy showed severe microvesicular and macrovesicular steatosis. The patient had been receiving stavudine and lamivudine for 6 months; both drugs were stopped. The patient survived but required prolonged hospitalization; antiretroviral therapy was reinstituted with nelfinavir/saquinavir/nevirapine.

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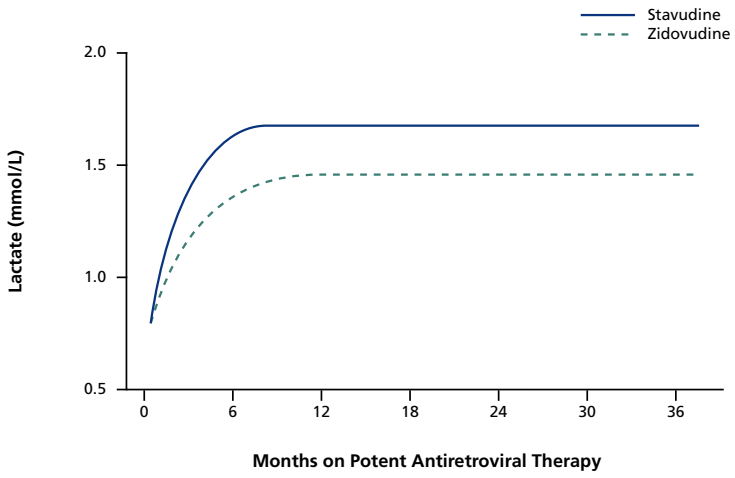

Figure **1.** Time to onset of lactemia from start of potent antiretroviral therapy including stavudine or zidovudine. Adapted from John et al, *AIDS,* 2001.

Severe Lactic Acidosis

The clinical syndromes potentially associated with lactemia and lactic acidosis include acute hepatitis (as exhibited by the patients in both case reports), fatty liver with steatosis, acidosis with shock, osteopenia, poor outcome in pregnancy, lipodystrophy, and peripheral neuropathy. Onset of acute hepatitis may occur weeks to months after starting nRTI therapy; symptoms include fatigue, dyspnea, nausea, vomiting, abdominal pain, and edema. In addition to hepatomegaly, encephalopathy and arrhythmia may be present. Laboratory findings include characteristic elevated liver function tests, and biopsy shows steatosis, necrosis, and inflammation. In one study, time to fat wasting was markedly accelerated in patients with lactemia compared with patients with normal lactate levels (White et al, *Antivir Ther,* 2000).

Management of severe lactemia includes withdrawal of nRTIs, with the time to return to normal lactate levels being on the order of 3 to 12 months. It is unclear whether nRTIs can or should be used in future treatment, although many practitioners would avoid stavudine or didanosine use. Patients with mild to moderate lactemia are at risk for developing acidosis and hepatitis, as well as chronic liver disease, lipodystrophy, and neuropathy, but it cannot be predicted in which patients these disorders may ultimately occur. It currently is recommended that serum lactate not be monitored routinely in every patient receiving nRTI therapy. However, monitoring should be performed in those patients with such symptoms as fatigue, nausea, and vomiting and in those with hepatitis, lipoatrophy, osteopenia, or history of lactic acidosis, those exhibiting anion gap or low HCO_3 levels, and pregnant patients. In addition to stopping nRTI administration in those with severe lactemia, it is recommended that nRTIs be stopped in those with lactate levels of 5.0 to 10.0 mmol/L if symptoms or signs are present, and that other potential causes of lactemia be investigated in those with levels of 5.0 to 10.0 mmol/L without symptoms and in patients with levels of 2.0 to 5.0 mmol/L with or without symptoms while therapy is continued.

> It is recommended that nRTI administration be stopped immediately in cases of severe lactemia or moderate lactemia with symptoms

Bone Disease

Potential explanations for the hip pain in the patient in case history 1 include pathologic fracture due to osteopenia and avascular necrosis. The prevalence of osteopenia in HIV disease currently is unknown, although the disorder is being documented with increasing frequency. In one multivariate analysis, osteopenia was associated with both lactemia (odds ratio, 2.39; 95% confidence interval, 1.39-4.11) and lipoatrophy (odds ratio, 1.73; 95% confidence interval, 0.72-4.07). Thus far, pathologic fractures have not been reported with increased frequency among patients with HIV disease; however, there is concern that such reports will eventually begin to accumulate given the increasing recognition of osteopenia and osteoporosis in these patients. Currently, routine screening for osteopenia is not recommended. Potentially remediable causes of osteopenia should be sought, including cigarette smoking, inactivity, and hypogonadism. Management includes calcium supplementation and weight-bearing exercise. Neither growth hormone treatment nor oxandrolone treatment has been shown to be effective in improving bone density over 24 weeks of treatment.

More than 100 cases of HIV disease-associated avascular necrosis have been reported in small patient series in the literature. The hip is the most commonly affected site, although disease of the ankle, shoulder, and elbow also have been reported. The cause of avascular necrosis remains unknown. After diagnosing avascular necrosis in a group of HIV-infected patients referred for unexplained bone pain and noting a high number of hip replacement procedures among patients from practices of referring physicians, investigators at the National Institutes of Health performed a prospective study of the prevalence of avascular necrosis in HIV-infected subjects.

A total of 339 HIV-infected patients who reported no bone pain symptoms and 118 HIV-seronegative controls underwent MRI evaluation. Avascular necrosis of the hip was found in 15 HIV-infected individuals (4.4%) compared with none of the control subjects (P = .015). Analysis of potential risk factors among the HIV-infected patients showed significant associations of avascular necrosis with testosterone use (relative risk [RR], 3.9; P = .01), corticosteroid use (RR, 3.8; P = .02), body building or long-distance running (RR, 3.3; P = .03), and use of lipid-lowering agents

(RR, 4.7; P = .004). Disease shown on MRI typically consisted of large lesions, with bilateral disease in many patients. The hip was the site of disease in the vast majority of cases, although necrosis of the knee, ankle, clavicle, and other bones was also observed. It remains unclear whether the factors associated with avascular necrosis in this study are causal factors. To date, no case of avascular necrosis has been observed in an HIV-infected patient who was not receiving antiretroviral therapy.

> Asymptomatic avascular necrosis of the hip was found in 4.4% of HIV-infected patients in one prospective study

The patient discussed in case history 1 had no resolution of hip pain and was found to have avascular necrosis on MRI evaluation, with the lesion becoming evident on plain x-ray film 1 month later. Within 1 year, the patient underwent total hip replacement.

The finding of a high prevalence of asymptomatic avascular necrosis in HIV-infected patients is disturbing. The potential for an association of osteonecrosis with increased survival duration, increased duration of exposure to antiretroviral drugs, or increased exposure to other drugs used by HIV-infected patients is suggested by the increasing frequency of reports of such disease in the literature and by findings indicating an increasing frequency of diagnosis of disease. The frequency of osteonecrosis in HIV-infected individuals in the Johns Hopkins HIV Clinic Cohort has increased substantially from 1995 to 2000 (Keruly et al, 8th CROI, 2001), from 0 to 4.8 per 1000 person-years.

It currently is uncertain what steps might be taken for prevention of the disorder. The natural history of asymptomatic lesions is unclear, although it is evident that patients do not necessarily become symptomatic within months of diagnosis. With regard to the risk factors identified in the prospective study, there is reluctance to suggest that patients with small asymptomatic lesions should discontinue testosterone therapy or weight-bearing exercise, since a causal relationship with the disorder has not been established and since both testosterone and exercise may be associated with other quality of life benefits. Similarly, it is unclear what recommendations should be made with regard to altering antiretroviral treatment. Currently, therapeutic options are limited to analgesia and assisted walking. Joint decompression frequently is performed; however, current experience does not convincingly show that this measure has a beneficial effect on the natural history of hip avascular necrosis or delays the time until joint replacement is necessary.

Summary

More information on the causes of and optimal management for lactemia and lactic acidosis and bone diseases in patients with HIV disease is desperately needed. Currently, it is known that lactemia is more common than lactic acidosis in HIV-infected patients, but the progression from the former to the latter is unpredictable. Monitoring of lactate levels to permit timely withdrawal of potentially offending nRTI drugs is recommended for patients with elevated lactate levels and symptoms or conditions that appear to indicate increased risk of acidosis, hepatitis, and other lactemia-associated clinical syndromes. The association of lactemia with bone disease suggests a common underlying role of mitochondrial dysfunction. However, the causes of osteopenia and avascular necrosis, both of which appear to be increasing in frequency among HIV-infected individuals, remain unclear. Improvements in prevention or management await a better understanding of the etiology of these disorders.

Presented in March 2001; reviewed and updated by Dr Masur in June 2001.

Grant Support and Financial Disclosure: Dr Masur has no affiliations with commercial organizations that may have interests related to the content of this article.

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New Cholesterol and Triglyceride Evaluation and Treatment Guidelines Issued by the National Cholesterol Education Program

The *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)* contains major updates for clinical practice guidelines on the prevention and management of high cholesterol in adults, and may be of interest to practitioners currently caring for HIV-infected patients with lipid, insulin, or other metabolic abnormalities. Developed over 20 months by 27 panel members and consultants, the report updates earlier guidelines issued in 1988 and 1993. The new guidelines are expected to substantially expand the number of Americans being treated for high cholesterol, including raising the number on dietary treatment from about 52 million to about 65 million, and increasing the number prescribed a cholesterol-lowering drug from about 13 million to about 36 million. Key changes include:

- Better identification of those at high risk for a heart attack and more aggressive cholesterol-lowering treatment
- Use of lipoprotein profile as the first test for evaluation of a high cholesterol level
- A new threshold at which low levels of high-density lipoprotein becomes a major risk factor for heart disease
- A new set of "therapeutic lifestyle changes," which includes intensified use of nutrition, physical activity, and weight control to improve cholesterol levels
- Risk assessment: identifying a "metabolic syndrome" of risk factors linked to insulin resistance, which often occur together and dramatically increase the risk for coronary events
- More aggressive treatment for elevated triglycerides
- Advising against the use of hormone replacement therapy as an alternative to cholesterol-lowering drugs

A complete copy of the new guidelines is available online on the National Heart, Lung, and Blood Institute Web site at www.nhlbi.nih.gov.

This announcement is adapted from JAMA, *2001;285(19): 2486-2497.*