Lactic Acidosis and Hepatic Steatosis Associated with Use of Stavudine: Report of Four Cases

Kirk D. Miller, MD; Miriam Cameron, MD; Lauren V. Wood, MD; Marinos C. Dalakas, MD; and Joseph A. Kovacs, MD

Background: An association between use of zidovudine and didanosine and a rare but life-threatening syndrome of hepatic steatosis, lactic acidosis, and myopathy has been reported.

Objective: To describe the syndrome of hepatic steatosis, lactic acidosis, and myopathy in four patients taking stavudine.

Design: Case series.

Setting: A community hospital in Washington, D.C., and National Institutes of Health Clinical Center, Bethesda, Maryland.

Patients: Two men and two women with HIV-1 infection who were taking stavudine presented with lactic acidosis and elevated levels of aminotransferases. All patients required intensive care.

Measurements: Levels of lactic acid, alanine aminotransferase, aspartate aminotransferase, amylase, and lipase; computed tomography of the abdomen; liver biopsy (two patients); and muscle biopsy (two patients).

Results: Histologic findings consistent with mitochondrial injury confirmed the diagnosis of hepatic or muscle abnormality.

Conclusion: Because hepatic steatosis may be life-threatening, physicians should consider it as a possible cause of elevated hepatic aminotransferase levels among patients taking stavudine.

A n uncommon but life-threatening syndrome of severe hepatic steatosis and lactic acidosis among patients infected with HIV-1 was first described in the early 1990s (1–3). By early 1994, at least 40 such cases had been reported to regulatory authorities, and an association with use of zidovudine and didanosine was established (4). An underlying mechanism involving impaired replication of mitochondrial DNA was proposed (5).

Although stavudine (Zerit, Bristol-Myers Squibb, Princeton, New Jersey) is the second most widely prescribed antiretroviral nucleoside analogue (6, 7), it has rarely been associated with the syndrome of severe hepatic steatosis and lactic acidosis. We report on four patients who developed this syndrome while receiving an antiretroviral regimen containing stavudine.

Case Reports

In 1997, four patients who had taken stavudine for 3 to 15 months in combination with other antiretroviral drugs presented with severe lactic acidosis, elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and evidence of fatty infiltration of the liver on computed tomography (Table). Two patients had elevated levels of muscle enzymes and two had clinical, laboratory, and computed tomographic evidence of pancreatitis. Two patients underwent liver biopsy, which revealed hepatic steatosis, and two had muscle biopsy that showed evidence of mitochondrial myopathy (Figure). One patient (patient 2) had chronic hepatitis C; none had chronic hepatitis B.

Patient 1

A 63-year-old obese HIV-infected woman presented with a 1-month history of nausea, vomiting, and abdominal pain. She had severe metabolic acidosis (arterial blood pH, 7.12), a markedly elevated serum lactate level, hepatic steatosis, and pancreatitis (Table). On admission, therapy with stavudine and lamivudine, which the patient had been using for 6 months, was discontinued. After a complicated hospital course, much of which was spent in the intensive care unit, the patient recovered and began taking nelfinavir, saquinavir, and nevirapine. Her illness did not recur.

Patient 2

A 54-year-old obese HIV-infected man presented with a 3-month history of nausea, vomiting, and abdominal pain. He had severe metabolic acidosis (arterial blood pH, 7.12), an elevated serum lactate level, and hepatic steatosis (Table). Therapy with stavudine, lamivudine, and indinavir, which the patient had been taking for 15 months, was discontinued. After a complicated 3-week hospitalization, the patient began taking lamivudine, saquinavir, and nelfinavir. His illness did not recur.
Table. Summary of Four Patients*

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD4* Count</th>
<th>HIV-1 Viral Load</th>
<th>Medications at Hospital Admission</th>
<th>Findings on Abdominal Computed Tomography</th>
<th>Histologic Findings†</th>
<th>Abnormal Laboratory Values‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cells/mm³</td>
<td>copies/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>192</td>
<td>2598</td>
<td>Stavudine, lamivudine nevirapine; trimethoprim–sulfamethoxazole; omeprazole; losinopril</td>
<td>Liver density consistent with diffuse fatty infiltration; pancreatic enlargement and peripancreatic inflammation</td>
<td>Liver: severe microvesicular and macrovesicular steatosis</td>
<td>ALT: 92 U/L AST: 175 U/L Lactate: 13.6 mmol/L Amylase: 353 U/L Lipase: 791 U/L</td>
</tr>
<tr>
<td>2</td>
<td>184</td>
<td>&lt;400</td>
<td>Stavudine, lamivudine, indinavir; trimethoprim–sulfamethoxazole; famotidine</td>
<td>Liver density consistent with diffuse fatty infiltration; normal pancreas</td>
<td>Liver: severe microvesicular and macrovesicular steatosis</td>
<td>ALT: 43 U/L AST: 53 U/L Lactate: 7.1 mmol/L</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>3178</td>
<td>Stavudine, didanosine, nelfinavir</td>
<td>Liver density consistent with diffuse fatty infiltration; pancreatic inflammation and necrosis</td>
<td>Muscle (quadriceps): increased fat droplets in myocytes, cytochrome oxidase–negative fibers, degenerating fibers</td>
<td>ALT: 120 U/L AST: 166 U/L Creatine kinase: 11 995 U/L Aldolase: 15 U/L Lactate: 9.9 mmol/L Amylase: 561 U/L Lipase: 6150 U/L</td>
</tr>
<tr>
<td>4</td>
<td>243</td>
<td>&lt;500</td>
<td>Stavudine, lamivudine, saquinavir, ritonavir; interferon-α</td>
<td>Liver density consistent with diffuse fatty infiltration; normal pancreas</td>
<td>Muscle (quadriceps): increased fat droplets in myocytes, occasional “ragged-red” fibers</td>
<td>ALT: 356 U/L AST: 115 U/L Creatine kinase: 359 U/L Aldolase: 23 U/L Lactate: 4.3 mmol/L</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; AST = aspartate aminotransferase.
† Findings are reported for standard light microscopy of liver biopsy specimens and both light microscopy and electron microscopy of muscle biopsy specimens.
‡ Shown are the most abnormal values during the course of the illness. Normal serum values are as follows: ALT, 6–41 U/L; AST, 9–34 U/L; creatine kinase, 38–386 U/L; aldolase, 1–6 U/L; amylase, 18–93 U/L; lipase, 21–132 U/L; and lactate, 0.5–2.2 mmol/L.

Patient 3

A 16-year-old HIV-infected girl presented with a 3-day history of nausea, vomiting, and abdominal pain. She had severe metabolic acidosis (arterial blood pH, 7.33), an elevated serum lactate level, hepatic steatosis, pancreatitis, and myopathy (Table). Therapy with stavudine, didanosine, and nelfinavir, which the patient had been taking for 3 months, was discontinued; the patient had previously taken didanosine for 4 years without problems. After a complicated hospital course that included a prolonged stay in the intensive care unit, the patient began receiving zidovudine, nevirapine, and nelfinavir. Her illness did not recur.

Patient 4

A 43-year-old HIV-infected man presented with a 2-week history of nausea, vomiting, and diffuse myalgias. His serum lactate level was elevated, and he had hepatic steatosis and myopathy (Table). Therapy with stavudine, lamivudine, saquinavir, and ritonavir was discontinued. The patient had taken stavudine for 15 months, lamivudine for 16 months, ritonavir for 9 months, and saquinavir for 2 weeks. Over the ensuing 4 weeks, his symptoms and laboratory abnormalities gradually resolved; he then began receiving a new antiretroviral regimen consisting of didanosine, lamivudine, and nelfinavir. His illness did not recur.

Discussion

We report on four patients in whom a syndrome of hepatic steatosis and lactic acidosis developed while they were taking stavudine as part of multidrug antiretroviral regimens. Two of the three patients who were also taking lamivudine at the onset of lactic acidosis subsequently restarted therapy with this drug without recurrence of their illness. One patient was also taking didanosine but had previously taken this drug without recurrence. We therefore believe that hepatic steatosis and lactic acidosis were most likely caused by stavudine. Although stavudine (and the other nucleoside analogues) do not have pharmacokinetic interactions that are likely to contribute to the development of hepatic steatosis and lactic acidosis, the possibility that combinations of agents of this class have additive metabolic toxicity cannot be excluded (8). Two patients developed concurrent acute pancreatitis, and two had biopsy-documented myopathy with prominent lipid accumulations due to mitochondrial dysfunction. Patients who...
develop acute pancreatitis as part of the syndrome seem to be at particular risk for severe disease and fatal outcome (9).

Initial symptoms may be mild and nonspecific, such as nausea and abdominal discomfort; this may lead to a delay in diagnosis until patients are severely ill (10). Of note, hepatic steatosis may be severe despite near-normal ALT and AST levels, and myopathy may be present with only modest elevations of creatine kinase level (1, 2, 9, 10).

Two of our patients were obese. Obesity is associated with nonalcoholic steatohepatitis, which may lead to hepatic fibrosis and cirrhosis (11). However, pancreatitis, myopathy, and lactic acidosis are not typical features of this entity. Moreover, the natural history of nonalcoholic steatohepatitis is one of chronicity and poor response to interventions; in contrast, the clinical course of our patients improved after withdrawal of stavudine therapy. It is interesting, however, that nonalcoholic steatohepatitis is predominantly found in women and that women seem to be disproportionately affected by nucleoside analogue–associated toxicity (1–3, 5–7, 9, 10, 12).

A similarity to the Reye syndrome was noted in a 1990 report that described a probable case of zidovudine-associated hepatic steatosis (1). The patient in that report had used aspirin, but aspirin use has not been found to be a feature of nucleoside analogue–associated hepatic steatosis. Nor has alcohol abuse been found to be an associated feature. None of our four patients had used aspirin over the long term, and none consumed ethanol heavily.

Current evidence suggests that nucleoside analogue toxicity results in mitochondrial injury (13, 14). The earliest signs of mitochondrial dysfunction, which precede structural abnormalities, include reduction of cytochrome oxidase and impaired β-oxidation of fatty acids that lead to accumulation of fat droplets within cells. Mitochondrial abnormalities due to nucleoside analogues were first described among HIV-infected patients who developed myopathy after long-term therapy with zidovudine (15). Subsequently, the “full” syndrome of hepatic steatosis, lactic acidosis, and mitochondrial myopathy was described (2, 16). Studies showed that use of nucleoside analogues led to depletion of mitochondrial DNA by selective inhibition of DNA polymerase-γ, which is responsible for replication of mitochondrial DNA (17). Depletion of mitochondrial DNA leads to depletion of components of the oxidative phosphorylation system, which in turn leads to a defect in pyruvate metabolism that favors production and accumu-
Hepatic Steatosis Associated with Stavudine Use

Brief Communication

Timely confirmation of mitochondrial dysfunction as the mechanism underlying the syndrome of hepatic steatosis, lactic acidosis, and mitochondrial myopathy was facilitated by the intensive investigation that followed the outcome of a 1993 trial of an investigational nucleoside analogue used to treat chronic hepatitis B (20). Whether a given nucleoside analogue causes a highly prevalent and acute catastrophic illness, as did fialuridine, or a relatively rare syndrome of the type described in this report seems to depend on minor differences in molecular structure. Such differences dictate whether an agent will be incorporated into replicating mitochondrial DNA (as in the case of fialuridine) or whether it will lead to termination of replication (as in the case of zidovudine, didanosine, and stavudine) (13).

As antiretroviral regimens have become more complex, elevations in ALT and AST levels have become common, especially in patients with concomitant hepatitis B or C infection. Current guidelines for the use of antiretroviral drugs recommend that HIV-1 viral loads and CD4+ T-lymphocyte counts be monitored every 3 to 4 months. Physicians should consider using these opportunities to also monitor ALT and AST levels. Because hepatic steatosis may be life-threatening, physicians should consider it as a possible cause of newly elevated ALT and AST levels among patients using stavudine as well as among those using zidovudine or didanosine. Elevated ALT and AST levels require closer monitoring; levels of serum lactate and pancreatic and muscle enzymes should be measured when significant elevations in ALT and AST levels are noted, and these tests should be considered when patients present with nonspecific gastrointestinal or abdominal symptoms. Computed tomography or ultrasonography can reliably identify fatty liver. Prospective studies are needed to define the incidence of hepatic steatosis and to determine whether patients with an isolated imaging finding of fatty liver are at higher risk for the syndrome described in this report.

In the absence of additional data, physicians should consider changing the nucleoside analogue component of antiretroviral regimens if patients have evidence of persistent hepatic steatosis. Furthermore, it seems prudent to temporarily discontinue therapy with all antiretroviral drugs in patients with lactic acidosis and associated hepatic steatosis, myopathy, or pancreatitis. On the basis of limited experience, it seems that therapy with antiretroviral agents, including nucleoside analogues, can be reinstituted after resolution of symptoms as long as the agent responsible for the syndrome is excluded.

From Warren Grant Magnuson Clinical Center, National Institute of Allergy and Infectious Diseases Intramural AIDS Program, National Cancer Institute, and National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland; and Kaiser Permanente Mid-Atlantic and West End Medical Center, Washington, D.C.

Requests for Single Reprints: Kirk D. Miller, MD, Critical Care Medicine Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, Building 10, Room 8C410, Bethesda, MD 20892.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Dr. Miller: Critical Care Medicine Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, Building 10, Room 8C410, Bethesda, MD 20892. Dr. Cameron: Division of Infectious Diseases, Kaiser Permanente West End Medical Center, 2100 Pennsylvania Avenue NW, Washington, DC 20037. Dr. Wood: National Cancer Institute, National Institutes of Health, Building 10, Room 13N240, Bethesda, MD 20892. Dr. Dalakas: National Institute of Neurological Diseases and Stroke, National Institutes of Health, Building 10, Room 4N248, Bethesda, MD 20892. Dr. Kovacs: Critical Care Medicine Department, Warren Grant Magnuson Clinical Center, Building 10, Room 7D43, National Institutes of Health, Bethesda, MD 20892.

Critical revision of the article for important intellectual content: K.D. Miller, M. Cameron, L.V. Wood, M.C. Dalakas, J.A. Kovacs.
Final approval of the article: M. Cameron, M.C. Dalakas, J.A. Kovacs.
Provision of study materials or patients: K.D. Miller, M. Cameron, L.V. Wood, M.C. Dalakas.
Collection and assembly of data: K.D. Miller, M. Cameron, L.V. Wood, M.C. Dalakas.

References