Lactic Acidosis Associated with Stavudine Administration: A Report of Five Cases

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Type “B” lactic acidosis has been described in patients receiving the nucleoside analogs zidovudine, didanosine, and fialuridine. Lactic acidosis has also been described in 4 patients receiving combination therapy with stavudine and lamivudine. We describe the development of chronic type “B” lactic acidosis in 3 patients receiving stavudine as a single agent and in 2 patients receiving combination therapy with stavudine and either lamivudine or delavirdine, a nonnucleoside analog. All patients presented with abdominal pain, vomiting, and hepatic steatosis. Other signs of mitochondrial toxicity included pancreatitis and myopathy (2 cases). The mean duration of stavudine therapy was 9.4 months, and the mean observed peak lactate level ± SD was 10.3 ± 5 mmol/L. After discontinuation of stavudine treatment, lactic acidosis improved in 4 patients after 4–60 weeks, and 1 patient died. Evaluations for other causes of lactic acidosis, including hypoxemia, malignancy, sepsis, and cardiogenic shock, were negative.

Type “B” lactic acidosis is a rare but potentially life-threatening complication of nucleoside analog therapy and is often accompanied by other serious clinical manifestations of mitochondrial toxicity, such as hepatic steatosis, pancreatitis, and myopathy. This syndrome has been reported with single nucleoside analog therapy with zidovudine, didanosine, or fialuridine and with combination therapy with lamivudine and stavudine [1–5]. We report 5 cases of stavudine-associated lactic acidosis; 2 are described in detail, and 3 additional cases are summarized in table 1.

Case 1

A 35-year-old HIV-infected woman presented with epigastric pain, vomiting, and loose stools for 2 weeks (table 1). The duration of stavudine therapy was 1 year, but it was discontinued 1 week before admission. Vital signs were blood pressure of 130/82 mm Hg, pulse rate of 130, respiratory rate of 24, and temperature of 39°C. Physical examination was significant for mild epigastric tenderness. Laboratory studies disclosed the following significant values: arterial pH, 7.42; PCO2, 33 mm Hg; PO2, 86 mm Hg (21% of FiO2); serum bicarbonate, 15 mmol/L; lactate, 10.3 mmol/L; albumin, 3.2 g/dL; amylase, 50 U/L; lipase, 27 U/L; lactate dehydrogenase, 450 U/L; alanine aminotransferase, 450 U/L; aspartate aminotransferase, 95 U/L; alkaline phosphatase, 46 U/L; and total bilirubin, 0.7 U/L. CT of the abdomen revealed fatty liver. All other laboratory studies including bacterial and acid-fast bacillus cultures of blood, urine, and stool were negative. Intravenous fluids, including a bicarbonate-containing solution, were administered, and the patient was discharged 27 days later with a serum lactate level of 3.8 mmol/L.

Case 2

A 34-year-old HIV-infected man presented with acute pancreatitis and lactic acidosis (table 1). His chief complaints were abdominal pain, anorexia, and vomiting for 2 weeks. The duration of stavudine therapy was 10 months. Vital signs were blood pressure of 160/100 mm Hg, pulse rate of 150, respiratory rate of 42, and temperature of 39°C. Physical examination was significant for markedly tender abdomen with reduced bowel sounds. Laboratory studies disclosed the following pertinent values: arterial pH, 7.30; PCO2, 24 mm Hg; PO2, 104 mm Hg (50% of FiO2); serum bicarbonate, 20 mmol/L; lactate, 10 mmol/L; albumin, 2.9 g/dL; amylase, 277 U/L; lipase, 1455 U/L; lactate dehydrogenase, 590 U/L; alanine aminotransferase, 41 U/L; aspartate aminotransferase, 62 U/L; alkaline phosphatase, 41 U/L; total bilirubin, 2 U/L; and direct bilirubin, 0.7 U/L. The WBC count was 12,200/µL, with 62% neutrophils. CT scan of the abdomen revealed fatty liver and pancreatitis. All other laboratory studies at admission, including bacterial cultures of blood, sputum, and urine, were negative. Treatment...
included intravascular volume expansion with use of a bicarbonate solution, broad-spectrum antibiotics, and thiamine. On hospital day 2, hemorrhagic pancreatitis with fat necrosis was found during exploratory laparotomy. Chronic lactic acidosis persisted, despite adequate oxygenation and systemic blood pressure. *Staphylococcus aureus* pneumonia and a wound infection, from which both *S. aureus* and *Enterococcus faecalis* (day 4) were isolated, complicated the hospital course. Eventually, hepatic and renal failure ensued, and the patient died on day 24. The serum lactate level 4 days before his death was 8.5 mmol/L. An autopsy confirmed acute pancreatitis with extensive fat necrosis and massive hepatomegaly with steatosis. Additional findings included early adult respiratory distress syndrome, lung atelectasis, and acute tubular necrosis of the kidneys. Cardiac examination revealed dilated heart chambers with “wavy” myocytes and interstitial edema (without evidence of coronary disease). A diffuse, multiorgan mononuclear cell infiltrate was also present; however, no evidence of malignancy or infectious disease was found.

**Discussion**

All 5 cases of stavudine-associated lactic acidosis reported here were characterized by complex acid-base disturbances; however, a finding common to all was lactic acidosis presenting with abdominal pain, anorexia, nausea, and hepatic steatosis. There was no evidence to support other etiologies of lactic acidosis at presentation, such as sepsis, hypoxemia, alcohol intoxication, malignancy, or metformin use. Therapeutic intervention included the discontinuation of all antiretroviral agents and the administration of iv fluids and bicarbonate.

Nucleoside triphosphates are preferentially incorporated into the newly transcribed viral DNA in place of thymidine and act as chain terminators, thereby inhibiting the viral RNA-directed DNA polymerase. Although mammalian nuclear DNA polymerase-α is not affected by the nucleoside analogs, they have been shown to exert an inhibitory effect on mammalian mitochondrial DNA polymerase-γ, an enzyme required for mitochondrial DNA replication. The potency order of various nucleoside analogs with regard to their inhibitory effect on mitochondrial DNA production and cell viability is as follows: zalcitabine > stavudine > zidovudine > didanosine [6].

Ultimately, 2 important mitochondrial catabolic pathways become impaired: pyruvate oxidation by pyruvate dehydrogenase and fatty acid oxidation via β-oxidation. In this milieu, the metabolic fate of pyruvate is shifted toward lactate production, and fatty acids are converted to triglycerides that accumulate in the hepatocyte cytoplasm. The nonnucleoside reverse transcriptase inhibitors, such as delavirdine, bind directly to viral DNA polymerase, thereby disrupting the enzyme’s catalytic site. The effect of nonnucleoside reverse transcriptase inhibitors on mammalian mitochondrial DNA polymerase-γ remains to be determined. Lactic acidosis has not been reported to be associated with acyclovir or ganciclovir, which are also nucleoside analogs, and the reason for this is unclear.

Why only a minority of patients develop mitochondrial toxicity when exposed to nucleoside analogs remains to be elucidated. Acquired deficiencies in riboflavin and thiamine, cofactors required for oxidative phosphorylation, may predispose to the development of lactic acidosis [5, 7]. Subtle defects in the mitochondrial oxidative enzymes, or other genetic factors, may also predispose a subset of patients to mitochondrial injury when they are exposed to nucleoside analogs. We hypothesize that the risk of developing mitochondrial toxicity is potentiated by the use of combination reverse transcriptase inhibitors; but the true risk remains to be determined. Patients receiving nucleoside analog therapy with stavudine, zidovudine, lamivudine, didanosine, and fialuridine should be carefully monitored for metabolic and hepatic abnormalities.

**References**


