Lactic Acidemia in Infection with Human Immunodeficiency Virus

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Lactic acidosis in patients infected with the human immunodeficiency virus was initially identified as a rare complication of therapy with nucleoside analog reverse transcriptase inhibitors (NRTIs). The only patient group that appears to be at greater risk is pregnant women. More recently, milder elevations in lactate (i.e., lactic acidemia or hyperlactatemia) have been found to be more common and to be associated with numerous illnesses. Mild asymptomatic lactic acidemia is common, but it appears to lead to more severe illness only rarely. This suggests that routine measurement of plasma lactate should be limited to patients with previous acidemia who reinitiate NRTI therapy and to pregnant women. For symptomatic lactic acidemia (generally >5 mmol/L), NRTIs and other antiretroviral therapy should be ceased. Currently, asymptomatic lactic acidemia should not be treated and should not lead to a change in antiretroviral therapy.

Lactic acidemia (defined by venous lactate >2.0 mmol/L) is common to several toxicities associated with nucleoside analog reverse transcriptase inhibitors (NRTIs) and nucleotide analog reverse transcriptase inhibitors that may have a mitochondrial pathogenesis [1]. Adenosine triphosphate forms of NRTIs and nucleotide analog reverse transcriptase inhibitors can inhibit mitochondrial DNA polymerase-γ, which could in turn lead to impaired synthesis of mitochondrial enzymes that generate adenosine triphosphate by oxidative phosphorylation of glucose and fatty acids [2, 3]. In vitro, this may manifest as increases in intracellular lactate, pyruvate, triglyceride, and fatty acids because neither glucose nor fatty acids can be oxidized normally.

Most NRTI-associated toxicities are relatively tissue- and drug-specific (table 1). The polymerase-γ hypothesis suggests that this specificity may be due to intracellular drug penetration and metabolism to the triphosphate form, to tissue-specific polymorphisms in mitochondrial DNA-γ, to the target tissue’s stores of natural nucleotides, and to the different dependency of specific tissues for mitochondrial function. In moderate and severe lactic acidemia, the target organ is thought to be the liver because of the associated biochemical, clinical, and pathological evidence of hepatic dysfunction in many patients [4–13]. It is unclear, however, whether milder lactic acidemia represents an increase in lactate production from one or more organs and/or decreased degradation.

PREVALENCE AND RISK FACTORS

Lactic acidemia with no or mild symptoms was detected in 8%–21% of patients receiving at least one NRTI versus 0%–1% of patients receiving no antiretroviral therapy [12, 14–17]. Symptomatic lactic acidemia is less common (~1.5%–2.5%). The incidence in 2 prospective studies was estimated to be 0.4–0.8 per 100 patient-years in adults. Mild acidemia does not appear to predict the development of subsequent more severe acidemia.

Most early cases of severe lactic acidemia were reported in women, but there are no firm data regarding differences by sex, race, or age. A report of 3 fatal cases of lactic acidemia in pregnant women receiving dual

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Clinical Infectious Diseases 2003;36(Suppl 2):S96–100
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1558-4388/2003/3607S2-0008$15.00
### Table 1. Known and possible mitochondrial toxicities of nucleoside analogue HIV reverse transcriptase inhibitors and their associations with lactic acidemia.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical feature(s)</th>
<th>Laboratory findings</th>
<th>Lactic acidemia</th>
<th>Rate, %</th>
<th>Drugs administered&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Therapy&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Aggravated by&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatomegaly, nausea, ascites, edema, dyspnea, encephalopathy</td>
<td>Liver enzymes ↑</td>
<td>Yes</td>
<td>1–2.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>All</td>
<td>Riboflavin (?)</td>
<td>Azoles, rifamycin, NNRTIs, PIs</td>
</tr>
<tr>
<td>Muscle</td>
<td>Fatigue, myalgia, proximal weakness, wasting</td>
<td>Creatine kinase ↑</td>
<td>No data</td>
<td>17</td>
<td>AZT</td>
<td>—</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Heart</td>
<td>Dilated cardiomyopathy</td>
<td>—</td>
<td>No data</td>
<td>Rare</td>
<td>AZT</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nerve</td>
<td>Distal pain, numbness, paresthesia, legs and arms with reduced reflexes or power</td>
<td>—</td>
<td>Yes</td>
<td>10–30</td>
<td>ddC = ddT &gt; ddl &gt; 3TC</td>
<td>Tricyclic antidepressant valproate</td>
<td>Isoniazid, vinca alkaloid</td>
</tr>
<tr>
<td>CNS</td>
<td>Perinatal neurologic illness</td>
<td>—</td>
<td>Yes (including CSF)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fat</td>
<td>Peripheral lipatrophy, lipomata (?)</td>
<td>—</td>
<td>Sometimes</td>
<td>50</td>
<td>ddT &gt; others</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Asymptomatic rare fractures</td>
<td>—</td>
<td>Sometimes</td>
<td>20–40</td>
<td>Unknown</td>
<td>As in HIV-uninfected patients</td>
<td>—</td>
</tr>
</tbody>
</table>

**NOTE.** Modified from Carr et al. [1] with permission of the publisher. 3TC, lamivudine; d4T, stavudine; ddC, zalcitabine; ddl, didanosine; NNRTI, nonnucleoside reverse transcriptase inhibitor; AZT, zidovudine; PI, protease inhibitor; ↑, increase.

* Mitochondrial toxicity of abacavir (ABC) monotherapy has not been reported.
* Cessation of the causative drug is required for reversal; improvements are often slow and/or partial.
* A complete list of drugs that might aggravate mitochondrial toxicity is provided at [http://www.hivatis.org/trtgdlns.html#Adult](http://www.hivatis.org/trtgdlns.html#Adult) (accessed 31 August 2002).
* Asymptomatic elevations of liver transaminases (with normal bilirubin) are more common (5%–15%).
often not to levels common, although even in fulminant hepatic failure, these are but jaundice is rare. Modest elevations in liver enzymes are hepatomegaly, peripheral edema, ascites, and encephalopathy, of hepatic dysfunction are common and can include soft, tender duration a median of 4 months in one series). Features diac dysrhythmias. The onset is acute or subacute (with symp-
domestic distension, and pain, dyspnea, and preterminal car-
demia are fatigue, weight loss, myalgias, nausea and vomiting,
The primary clinical features of moderate to severe lactic aci-
drugs. There are no data implicating non-NRTIs or protease
simultaneous exposure to 3 NRTIs, the contribution of pre-
existing liver disease, and concomitant use of other hepatotoxic
There are no data implicating non-NRTIs or protease
inhibitors in the pathogenesis of lactic acidemia.

CLINICAL FEATURES

The primary clinical features of moderate to severe lactic aci-
demia are fatigue, weight loss, myalgias, nausea and vomiting, abdominal distension, and pain, dyspnea, and preterminal car-
dic dysrhythmias. The onset is acute or subacute (with symp-
tom duration a median of 4 months in one series). Features of hepatic dysfunction are common and can include soft, tender hepatomegaly, peripheral edema, ascites, and encephalopathy, but jaundice is rare. Modest elevations in liver enzymes are common, although even in fulminant hepatic failure, these are often not to levels >10-fold above normal, as with other forms of acute hepatic failure. Hepatic steatosis is a common finding on imaging studies and biopsy, with necrosis evident in more fulminant cases. Hypovolemia and sepsis, common causes of lactic acidemia, are not seen. Patients with low-level lactic acidemia (2–5 mmol/L) may present with a milder constitutional and hepatic illness but are often asymptomatic. Features of NRTI-induced peripheral neuropathy, another mitochondrial NRTI toxicity, may also be present and can include ascending neuromuscular weakness in some cases.

Overall mortality was 80% in patients with HIV-related lactic acidemia >10 mmol/L, whereas no deaths have been reported in those with lactate <10 mmol/L. Prognosis of lactic acidemia depends on the level at the time of diagnosis. In one study, lactate levels (mean, 4.2 mmol/L) returned to normal at a mean of 3 months after NRTI cessation [12]. Clinical features may take longer to resolve. Fatal chronic liver disease was described in one patient 2 years after complete clinical recovery from lactic acidemia with acute hepatitis [19], but the frequency of chronic disease is unknown.

Lactic acidemia has also been observed with other mito-
chondrial toxicities, namely myopathy and postpartum neuro-
logic toxicity [20–22]. Several studies have found associations between lactic acidemia and several other toxicities of unknown pathogenesis, peripheral lipoatrophy, peripheral sensory neu-
ropathy, and osteopenia [12, 16, 23–25]. Further, mild asymp-
tomatic lactic acidemia has been associated with more rapid onset of lipoatrophy [23], and 2 studies have demonstrated mitochondrial depletions within peripheral adipocytes from some patients with lipoatrophy, although a cause-and-effect relationship has not been proven [26, 27].

ASSESSMENT AND MONITORING

Diagnosis of NRTI-related lactic acidemia requires demonstration of increased lactate levels in the absence of other known causes, such as dehydration, vigorous exercise, sepsis, hypox-
emia, alcohol intoxication, renal failure, hyperthyroidism, and other drugs [28]. There is no universally accepted definition of severe NRTI-related lactic acidemia. On the basis of the high risk of serious morbidity or death, a threshold for severe aci-
demia might be a confirmed level >10 mmol/L regardless of the clinical presentation, or >5 mmol/L in the presence of related new symptoms and signs.

Care is required with sample collection and processing to avoid falsely elevated readings. Patients should be advised not to undertake vigorous exercise for 24 h beforehand and should be well hydrated at the time of blood collection. Blood should be collected without fist clenching—and, if possible, without stasis—into a prechilled, gray-top (fluoride-oxalate) tube, transported immediately on ice to the laboratory, and processed within 4 h of collection. An elevated lactate level should always be confirmed by repeat measurement with the patient rested and well hydrated, and other potential causes should be excluded before one or more NRTIs are considered to be the cause. Measurement of arterial pH confirms the presence of acidosis, but this may not be necessary in many instances.

Because no assay can predict who will develop lactic aci-
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demia, patients should be aware that symptoms of lactic acidemia are nonspecific and can occur at any time. In view of the absence of data correlating them with outcome, other measures of mitochondrial function, such as lactate-pyruvate ratio, cannot be recommended at this time.

It is unknown whether or how often plasma lactate should be measured. Routine measurement is justified at this time only in NRTI recipients with clinical features consistent with lactic acidemia, such as new-onset fatigue, dyspnea, weight loss or nausea, low bicarbonate, chloride, or albumin, raised anion gap, unexpected increases in liver enzymes, or new onset of clinical liver failure, as well as in pregnant women receiving NRTIs, and in those recommencing NRTIs who have had lactic acidemia previously (table 2).

TREATMENT

In all patients with confirmed lactate levels >10 mmol/L, as well as those with confirmed lactate levels >5 mmol/L who are symptomatic, all NRTIs should be discontinued if no other cause is evident (table 3). All concomitant antiretroviral drugs should be ceased at the same time to avoid development of HIV drug resistance. Non-NRTI or protease inhibitor therapy can be restarted after the lactate level normalizes and the associated illness resolves. Reinstitution of alternative NRTIs in patients with previous lactic acidemia may be possible in some individuals [14] but should be closely monitored, with lactate measured every 4 weeks for at least 3 months.

For symptomatic patients whose levels are <5 mmol/L, lactate levels should be measured regularly. For asymptomatic patients in whom lactate levels are 2–5 mmol/L, there is no evidence to suggest that any change in antiretroviral therapy is necessary, but there are also no long-term safety data indicating whether or not adverse consequences may occur at levels in this range.

There is no proven intervention for lactic acidemia apart from NRTI cessation. Several agents have been used with limited success in the treatment of lactic acidemia in the setting of congenital mitochondrial diseases [29]. These include essential vitamin coenzymes (thiamine and riboflavin), electron acceptors (coenzyme Q10 [ubiquinone]), antioxidants (vitamins C, E, and K), and L-carnitine. There are no adequate data suggesting a role for any of these agents in the treatment or prevention of NRTI-related lactic acidemia [30].

CONCLUSIONS AND FUTURE DIRECTIONS

Insufficient data exist as to the prevalence, type, diagnosis, and management of illnesses associated with lactic acidosis that may complicate NRTI therapy. Assays that predict or more readily diagnose such toxicities are needed. Therapies that will reduce the incidence and impact of lactic acidemia are required, as are newer, less toxic NRTI agents.

Table 3. Recommendations for the management of lactic acidemia in HIV-infected patients.

<table>
<thead>
<tr>
<th>Lactate, mmol/L</th>
<th>Symptoms of lactic acidemia</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>Any</td>
<td>Cease NRTIs if other causes not present</td>
</tr>
<tr>
<td>5–10</td>
<td>Yes</td>
<td>Repeat; cease NRTI therapy if still elevated and other causes not present</td>
</tr>
<tr>
<td>2–5</td>
<td>Yes</td>
<td>Repeat; dehydration or laboratory artefact likely</td>
</tr>
<tr>
<td>&lt;2</td>
<td>Yes</td>
<td>Watch carefully; cease NRTI therapy if symptoms are pronounced</td>
</tr>
</tbody>
</table>

NOTE. NRTI, nucleoside reverse transcriptase inhibitor. Recommence alternative NRTI therapy once lactate normalizes and illness resolves; and monitor lactate closely. Other known causes of lactic acidemia include dehydration, inappropriate sample collection, vigorous exercise, sepsis, hypoxemia, alcohol intoxication, renal failure, pancreatitis, hyperthyroidism, and other drugs (e.g., biguanides).

References


