Editorial Response: Hyperlactatemia and Hepatic Steatosis as Features of Mitochondrial Toxicity of Nucleoside Analogue Reverse Transcriptase Inhibitors

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The long-term toxicity of highly active antiretroviral therapy (HAART), especially the development of both the lipodystrophy syndrome and hyperlipidemia, has been linked to the use of HIV protease inhibitors in most studies. However, the broad spectrum of toxicities associated with one of the other classes of drugs, the nucleoside analogue reverse transcriptase inhibitors (NRTIs), can display complications almost as serious and with more fatal outcomes. The common pathway of NRTI toxicities is induction of mitochondrial dysfunction [1, 2], because NRTIs inhibit DNA polymerase-γ, an essential enzyme for the replication of mitochondrial DNA (mtDNA). Depletion of mtDNA will follow, successively leading to depletion of mtDNA-encoded proteins and to mitochondrial dysfunction. All long-term side effects of NRTIs that have been described can be attributed to this mitochondrial toxicity, and recently we hypothesized that the HAART-related lipodystrophy is induced via this mechanism as well [3].

See article by Lonergan et al. on pages 162±6.

The most dramatic presentation of mitochondrial toxicity is the development of acute lactic acidosis, which unfortunately has a fatal course in most cases. The initial clinical symptoms generally consist of unexplained nausea, profuse vomiting, and abdominal pain, sequentially followed by compensatory hyperventilation, liver failure, and arrhythmias [4, 5]. These symptoms have been described in association with zidovudine, didanosine, and stavudine therapy [5]. At present, no prospective studies on the occurrence of this syndrome have been undertaken. On the basis of an observational cohort, Fortgang et al. [6] estimated the incidence of this syndrome to be ≈1.3 cases per 1000 person-years of nucleoside exposure. This number is in accordance with our own experience (4 fatal cases within 1 year in the Netherlands, with 3000 treated patients; incidence, 1.3 cases per 1000 treated person-years [7]) and with Maulin et al. [8], who described 2 cases of acute lactic acidosis within 1.5 years in a cohort of 867 patients who were receiving antiretroviral therapy (incidence, 1.7 cases per 1000 treated person-years). In their article in this issue of Clinical Infectious Diseases, Lonergan et al. [9] calculate a much higher incidence (20.9 cases per 1000 treated person-years), but they correctly argue that they used a broader case definition. Only 4 of their patients had peak levels of serum lactate >5 mmol/L, of whom only 2 had very mild signs of acidosis (bicarbonate levels of 17 and 22 mmol/L). Using a broader case definition, Maulin et al. [8] also reported a higher incidence (25.2 cases per 1000 treated person-years).

To estimate the real incidence of the syndrome in NRTI-treated patients, data need to be collected systematically and prospectively, with clear case definitions. Given that it is doubtful whether lactate levels of 2–4 mmol/L are clinically significant, and that lactic acidosis is believed to become manifest only at lactate levels >5 mmol/L [10], I would suggest a discriminating terminology: mild hyperlactatemia (lactate level of 2.1–5 mmol/L), serious hyperlactatemia (lactate level ≥5 mmol/L), and lactic acidosis (lactate level ≥5 mmol/L and bicarbonate level <20 mmol/L). Using these definitions during a cross-sectional analysis of 211 HIV-infected patients, we found 39 cases (13.2% of patients) of mild hyperlactatemia and only 1 case (0.4% of patients) of severe hyperlactatemia (lactate level, 5.1 mmol/L; this had normalized when the patient was tested 2 weeks later). None of these cases had bicarbonate levels <20 mmol/L. Thirty-five (89%) of the patients with cases of mild hyperlactatemia and 1 with a case of severe hyperlactatemia were receiving NRTI therapy, and none had any clinical symptoms [11]. Because the measurement of lactate requires a standardized mode of sample-handling (fluorinated tubes, which should be put on ice and centrifuged immediately) and the clinical significance of mildly elevated levels is still unknown, routine measurements in asymptomatic patients should not be recommended, unless prospective studies have proven its predictive value. However, one should measure lactate and bicarbonate levels in patients who have the clinical symptoms described above.

Lactate is a normal metabolic end-product of glycolysis. It is formed when pyruvate reacts with reduced nicotinamide adenine dinucleotide (NADH) and is converted back to pyruvate by reactions with the oxidized counterpart of the dinucleotide (NAD⁺). Both reactions are catalyzed by the ubiquitous enzyme lactate dehydrogenase (LDH). Under normal aerobic conditions, pyruvate is further metabolized in the mitochondrion by oxidative phosphorylation to CO₂, H₂O, and ATP (figure 1). During this process, a favorable NADH-to-NAD⁺ ratio is cre-
glucose

\[ \text{pyruvate} \xrightarrow{\text{LDH}} \text{lactate} \]

\[ \text{NADH} \rightarrow \text{NAD}^+ \]

\[ \text{H}^+ \]

\[ \text{OXPHOS} \]

\[ \text{mitochondrion} \]

\[ \text{O}_2 \rightarrow \text{ATP} \]

Figure 1. Schematic representation of the cytosolic equilibrium between the conversion of pyruvate to lactate and the reconversion of lactate to pyruvate, mediated by the enzyme lactate dehydrogenase (LDH). When enough NAD$^+$ is produced during oxidative phosphorylation (OXPHOS), pyruvate levels increase relative to lactate levels.

ated, enabling a continuous flow from lactate to pyruvate. However, when oxidative phosphorylation is hampered (for instance, under anaerobic conditions, or as a result of defective mtDNA-encoded proteins), the increased NADH-to-NAD$^+$ ratio shifts the equilibrium of the LDH reaction toward lactate [10]. During resting conditions, but especially during exercise, skeletal muscle is the most important producer of lactate, but in normal situations the liver (~50%) and, to a lesser extent, the renal cortex (~20%) guarantee an efficient clearance of this lactate from the circulation [10], which leads to a stable lactate concentration of ~1 mmol/L. Persistent hyperlactatemia (measured under resting conditions), therefore, only develops when this clearance mechanism is hampered.

In that respect, the report of Lonergan et al. [9] adds an important element to our picture of hyperlactatemia: they demonstrate clear abnormalities in the livers of their patients with persistent hyperlactatemia. Of the 6 patients in their cohort who underwent biopsies, 5 had microvesicular or mixed hepatic steatosis, and the sixth had signs of active hepatitis B. Among another 5 patients who did not undergo biopsies, radiologic imaging suggested hepatic abnormalities in 3. All patients had elevated transaminase levels. Furthermore, in all 11 patients there was a very slow normalization of lactate levels after NRTI therapy was interrupted, which demonstrated a defect in the normal, rapid clearance mechanism of serum lactate. This slow normalization of elevated lactate levels was also described by Maulin et al. [8] for their cohort.

Increased lactate production can be induced either by an-aerobic glycolysis or by a defect in the oxidative phosphorylation of peripheral tissue (e.g., muscle), but the finding of a persistently elevated lactate concentration in patients who are receiving NRTI therapy is more a reflection of an impaired hepatic lactate clearance than of an increased production. The sole pathway for lactate utilization is conversion back to pyruvate, which depends on efficient oxidative phosphorylation in the liver. An impaired lactate-clearance, therefore, can only be the result of a mitochondrial dysfunction in the hepatocytes. On histopathologic evaluation, this dysfunction is shown by microvesicular hepatic steatosis, which results from an impaired β-oxidation of free fatty acids, a process that also relies heavily on normal oxidative phosphorylation [12]. The fact that a patient with chronic hepatitis B can have a decreased lactate-clearance shows that, apparently, other liver diseases might lead to similar disturbances.

If severe hyperlactatemia or lactic acidosis is found, administration of NRTIs should be interrupted immediately in order to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome. Furthermore, the addition of compounds, such as riboflavin, L-carnitine, or co-enzyme Q, seems to prevent a fatal outcome.

In summary, the mitochondrial toxicity of NRTIs can induce a diverse spectrum of clinical symptoms, but persistently elevated lactate levels are likely to occur only when the hepatic lactate-clearance mechanism is impaired. This can be caused by either NRTI-induced hepatic mitochondrial dysfunction itself or possibly by other chronic hepatic diseases. Future studies are needed to demonstrate the true incidence of the described features and to clarify their clinical significance, but also to develop treatment strategies, such as vitamin supplementation and alternative options for further antiretroviral therapy.

References


