Symptomatic hyperlactataemia and lactic acidosis in the era of highly active antiretroviral therapy

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The prognosis of patients infected with HIV type 1 has improved markedly since the advent of potent antiretroviral therapies (ARTs). ARTs have enabled sustained suppression of HIV replication, recovery of the immune system and a substantial decrease in the frequency of opportunistic infections. Antiretrovirals may, however, cause life-threatening complications which include lactic acidosis, pancreatitis, hypersensitivity reactions, liver toxicity and severe immune reconstitution inflammatory syndrome.

A subgroup of patients being treated with nucleoside reverse transcriptase inhibitors (NRTIs) will develop symptomatic hyperlactataemia and lactic acidosis, a manifestation of mitochondrial toxicity.

Using mechanisms similar to those used to inhibit viral replication, NRTIs also inhibit human mitochondrial DNA polymerase gamma.[1] This inhibition leads to a depletion of mitochondrial DNA and an alteration in the synthesis of mitochondrial proteins. Subsequently there is an accumulation of mutations within mitochondrial DNA; this may lead to clinical toxicities such as skeletal myopathy, cardiomyopathy, neuropathy, HIV-associated neuromuscular weakness syndrome, pancreatitis, hepatic steatosis and lactic acidosis.[2]

Some NRTIs have a greater affinity for DNA polymerase gamma and therefore cause lactic acidosis more commonly. Stavudine (d4T) and didanosine (ddI) have the greatest affinity, and tenofovir (TDF) and abacavir (ABC) the least (ddI > d4T > AZT > 3TC = ABC = TDF). The use of stavudine is the most frequently identified risk factor.[3]

Lactic acidosis and symptomatic hyperlactataemia can occur from 1 month to 20 months after commencing NRTIs.[4] Patients may be asymptomatic, have nonspecific symptoms or be critically ill. Typical initial symptoms may develop over 1 - 6 weeks[5] and include dyspnoea, abdominal complaints (vomiting, pain and distension), myalgia, fatigue and weight loss. There may also be associated lipodystrophy and axonal neuropathy. The development of these conditions will depend on the patient's adherence, duration of treatment, the specific NRTIs used and also the number of NRTIs in the regimen.

Several factors may predispose a patient to the development of lactic acidosis/hyperlactataemia. These include female sex, excellent compliance, duration of treatment of more than 6 months, chronic muscle or kidney disease, chronic hepatitis B or C infection, and the combination of d4T and ddI, especially in pregnancy.[5-7] The correlation between women with an increased body mass index (BMI) and lactic acidosis remains unproven. Conditions unrelated to NRTI administration may also cause lactic acidosis (Table I) and this differential must always be considered in all patients who present with raised serum lactate levels.

Table I. Conditions causing raised serum lactate in the absence of NRTI use[6,7,9]

Increased energy levels	Exogenous intoxication
Exercise	Salicylates
Infection (sepsis)	Biguanides
Decreased lactate clearance	Isoniazid
Kidney disease	Cyanide
Liver disease	Methanol
Malignancy	Shock/hyperperfusion states

There is no consensus on criteria or definitions with regard to raised serum lactate concentrations. Hyperlactataemia is commonly referred to as one of three clinical and biochemical entities.

1. **Asymptomatic hyperlactataemia (subclinical hyperlactataemia).** Here the lactate level is mildly or moderately raised (2.5 - 5 mmol/l, depending on preferred criteria) and the patient is asymptomatic.[8] Up to 25% or more of patients treated with NRTIs will have an elevated lactate concentration during their course of treatment, but most (85%)

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remain symptom free.[9] Hyperlactataemia may be transient or prolonged and has not been found to predict the onset of symptomatic or severe lactic acidosis.[10] Therefore screening asymptomatic patients on NRTIs is not considered beneficial.[8] The variability in lactate measurements may reflect differences in venous sampling techniques.[9]

2. **Symptomatic hyperlactataemia.** In this category patients have moderately elevated lactate levels (2.5 - 5 mmol/l), no acidosis, but are symptomatic.[10] The prevalence of this condition is approximately 8 - 14.5 per 1 000 patient-years.[9] This may be an early manifestation before the onset of acute severe lactic acidosis. Withdrawal of ARTs at this stage usually leads to good clinical recovery indicating the significance of an early diagnosis.[9]

3. **Lactic acidosis.** The criteria used to diagnose lactic acidosis include serum lactate > 5 mmol/l, bicarbonate level < 20 mmol/l, arterial pH < 7.34 and anion gap > 12. The incidence varies from centre to centre but is thought to be in the region of 1 - 5 per 1 000 patient-years.[7] These patients are usually symptomatic and the mortality rate is high. A serum lactate concentration of > 10 mmol/l is considered an independent predictor of mortality and a level > 15 mmol/l is associated with > 60% mortality.[4]

For an accurate lactate measurement the specimen must be collected from an uncuffed arm, in a fluoride tube, put on ice immediately and sent to the laboratory within 4 hours. A second specimen should be taken to confirm an elevated lactate. The patient should be well hydrated and should not exercise for 24 hours before sampling.[11]

In resource-poor settings where this is not possible calculating the anion gap will be helpful as this may alert one to the presence of a raised serum lactate (anion gap = (Na + K) – (HCO^3 + Cl)).[1] A normal anion gap ranges from 6 to 12 mmol/l.

On admission, arterial blood gases, urea and electrolytes and surrogate markers should be monitored. Surrogate markers include lactate dehydrogenase (LDH), creatinine kinase (CK), amylase, lipase and transaminases.[11] The patient should be assessed for other signs of mitochondrial toxicity including peripheral neuropathy and lipoatrophy. An abdominal ultrasound and/or computed tomography (CT) scan should be performed if pancreatitis is suspected and a liver biopsy should be considered to confirm a diagnosis of possible hepatic steatosis.

In those patients with symptomatic hyperlactataemia or lactic acidosis all antiretroviral medication must be discontinued.[9] The need for hospital admission depends on the severity of symptoms, presence of acidosis and lactate levels. Owing to the long half-life of mitochondria (4.5 - 8 weeks) the time required for clinical recovery ranges from 4 to 28 weeks.[11]

Management is predominantly supportive, namely intravenous fluid rehydration, dialysis and respiratory support. There is little evidence to support or negate the administration of sodium bicarbonate. Administration of essential co-factors such as thiamine, riboflavin, L-carnitine, vitamin C and antioxidants have been used anecdotally.[4,12] Several published case reports describing the use of different co-factors at different dosages suggest they may induce recovery from lactic acidosis.[4] The experience with riboflavin seems the most extensive.[11] However, no adequate controlled trials exist to support this.

Although the safest treatment option for patients when ready to be re-challenged with ARTs would be a NRTI-sparing regimen, i.e. the combination of a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor, switching to another NRTI after recovery may be justified. NRTIs such as TDF, ABC, 3TC and AZT have a lower affinity for DNA polymerase gamma and have been used safely.[3,11] This may be an option where fewer antiretroviral drugs are available (public sector) or in those patients with limited treatment options. In these selected cases NRTIs with a lower affinity may be initiated once lactate measurements have been found to be within the normal range for 2 - 3 months. Subsequent close monitoring of lactate levels will be necessary.

In South Africa, as ARTs become more utilised and d4T-containing regimens remain the first line of treatment, the prevalence of NRTI-related mitochondrial toxicity can be expected to increase significantly. The clinician must be aware of the risk factors and have a high index of suspicion for these syndromes in every patient on NRTI therapy. Policy makers will have to seriously consider the swift registration of newer and safer antiretroviral drugs available on the international market and it will become necessary for drug companies to find innovative ways to make these drugs available to communities with limited financial resources.

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