Lactic Acidosis in an Infant Receiving HIV Prophylaxis

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Zidovudine is safe and effective in reducing transmission of HIV from mother to infant but rare serious side effects do occur. Is it worth the risk?

vertical transmission of human immunodeficiency virus (HIV) has dramatically decreased with the administration of antiretroviral treatments (ART) to HIV-infected mothers and their infants. The Pediatric AIDS Clinical Trials Group 076 (PACTG 076) originally showed zidovudine, a nucleoside analogue reverse transcriptase inhibitor (NRTI), to be a safe and effective therapy in preventing vertical transmission when administered to both mother and child.1 Guidelines currently recommend zidovudine for HIV prophylaxis for 4-6 weeks for neonates exposed to HIV in utero.2 Despite the overall safety findings of zidovudine from PACTG 076, rare, but serious, side effects have been observed. Although data are conflicting, NRTIs have been linked to mitochondrial toxicity that leads to lactic acidosis, cardiac abnormalities, neurologic delays, and death.3-5 We present a case of presumed mitochondrial toxicity and lactic acidosis in an infant exposed to zidovudine for HIV prophylaxis.

Patient presentation
A 5-week-old female born to an HIV-positive mother presented to a referring hospital for excessive vomiting of 2 days’ duration. Emesis was reported to occur after each feed and was non-bloody, non-bilious, and non-projectile. She had been afebrile with no sick contacts. She did have a history of reflux and would have small spit-ups after each feed. Diet consisted of infant formula 2-4 oz every 2-4 hours, mixed appropriately. Prenatal history was notable for maternal HIV diagnosed 16 years prior to the pregnancy; the mother, however, did not start HAART until pregnancy was confirmed. Treatment was initiated with elvitegravir/cobicistat/emtricitabine/tenofovir 6 months prior to her giving birth. She received IV zidovudine intrapartum, and the patient was delivered by scheduled C-section at 39 weeks gestation. Infant was given oral zidovudine 4 mg/kg/dose every 12 hours within 6 hours of birth and scheduled to continue for a 6-week total course.

On presentation, results of the infant’s laboratory studies were notable for a CO₂ of 17 mEq/L. BUN, creatinine, and liver enzymes were all within normal limits. Lactic acid levels were initially reported at 6.2 mmol/L, repeated, and levels remained elevated at 5.3. LDH was 345 U/L, venous pH 7.29,
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and pCO₂ 40 mmHg. CBC value was reassuring. Results of abdominal X-ray and pyloric ultrasound were unremarkable. Rapid testing for influenza and respiratory syncytial virus were negative. Urine and blood cultures were sent. Patient received a 15 mL/kg IV fluid bolus and was transferred to our hospital for further evaluation of metabolic acidosis.

Upon admission, zidovudine was stopped given that the patient was close to completing the 6-week course and hyperlactatemia was present. The patient was monitored as an inpatient for 3 days and had no further vomiting episodes. Results of blood and urine cultures drawn at the referring hospital were reported negative and HIV testing was negative. Repeat labs were completed on the day of discharge and showed elevated potassium and bicarbonate slightly low at 18. Venous blood gas showed pH 7.41 and lactate 1.1. Urine electrolytes were sent for evaluation of possible renal tubular acidosis type 2, but given normal pH on repeat venous blood gas this diagnosis was ruled out. Patient was discharged with close follow-up by primary care.

Next: Hyperlactatemia and lactic acidosis, discussion

Discussion

Hyperlactatemia and lactic acidosis due to mitochondrial toxicity are known side effects of NRTIs and have been described in HIV-uninfected children exposed perinatally to zidovudine. NRTIs inhibit HIV reverse transcriptase and prevent intracellular replication of viral DNA. However, these medications also inhibit DNA polymerase γ, which leads to a disruption in oxidative metabolism.

Energy production then relies on anaerobic metabolism shifting the pyruvate-lactate balance towards lactate:

\[
\text{pyruvate} + \text{NADH} + \text{H}^+ \leftrightarrow \text{lactate} + \text{NAD}^+
\]

Early signs of increased lactate levels include nausea and vomiting, loss of appetite, abdominal pain, fatigue, peripheral neuropathy, and weight loss. Without discontinuation of the offending agent, followed by treatment, symptoms can worsen and patients can experience fulminant hepatic, pancreatic, or respiratory failures. Mitochondrial injury affects tissues with high energy requirements, such as CNS and muscle, potentially leading to neurologic delays and/or cardiac issues.

Chronic, mild hyperlactatemia is common

Up to 30% of children receiving NRTI therapies are expected to experience chronic, mild hyperlactatemia with lactate levels ranging from 2.1–5.0 mmol/L. The clinical significance of this finding is unknown as these patients are commonly asymptomatic. However, rare, sometimes fatal, cases of symptomatic lactic acidosis and neurologic dysfunction have also been reported. Blanche et al retrospectively analyzed 1754 children exposed to zidovudine alone or in combination with lamivudine. They identified 8 patients who had mitochondrial dysfunction, 5 of whom had persistently elevated lactate levels and presented with delayed neurologic symptoms and 2 of whom died.

Noguera and colleagues prospectively evaluated 127 HIV-uninfected infants born to HIV-infected mothers of whom 96% were exposed to zidovudine alone after birth. They found 63 patients to have elevated lactate levels at least once during the 12-month study period, but 44 of those patients had normalized lactate levels at 1 year of age. They noted 3 patients to have
neurologic deficits consistent with mitochondrial toxicity, but no cases of lactic acidosis were reported.4

**Treatment recommendations vary**

Guideline recommendations for NRTI-induced hyperlactatemia and lactic acidosis treatment vary depending on lactate levels. For confirmed levels ranging 2.1–5.0 mmol/L, ART can be temporarily held and an alternative ART can be considered.2 In children with lactate levels > 5.0 mmol/L confirmed with second tests or >10.0 mmol/L on any single test, ART must be discontinued and the acidosis managed based on patient presentation.2 Vitamins, riboflavin and thiamine, and antioxidants, coenzyme Q-10 and L-carnitine, have shown benefit in small case reports, but currently have no randomized controlled trials to support their use.

Given the proven benefit in reduction of HIV transmission with zidovudine administration in the perinatal period there is little debate in regards to whether pediatric patients should receive this medication. However, it is important for clinicians to be aware of this potential life threatening side effect and have a high suspicion to obtain lactate levels in children on prophylactic zidovudine.

**References:**


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