NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR ASSOCIATED LACTIC ACIDOSIS CONFUSING DIABETIC KETOACIDOSIS.

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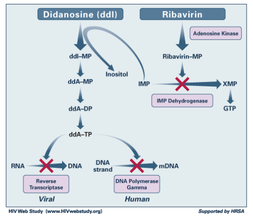
INTRODUCTION

Lactic acidosis secondary to mitochondrial toxicity is a rare and potentially fatal complication of antiretroviral therapy involving nucleoside reverse transcriptase inhibitors (NRTIs). It is important that clinicians recognize this entity and its etiology as early as possible so that a treatment plan may be instituted that may halt the progression and resolve this process. The outcome of NRTI induced lactic acidosis is frequently fatal, and there are very few published reports of treatment regimens that have had success. We present the case of a 56 year old HIV positive woman who developed severe lactic acidosis during her hospitalization while on NRTIs.

CASE PRESENTATION

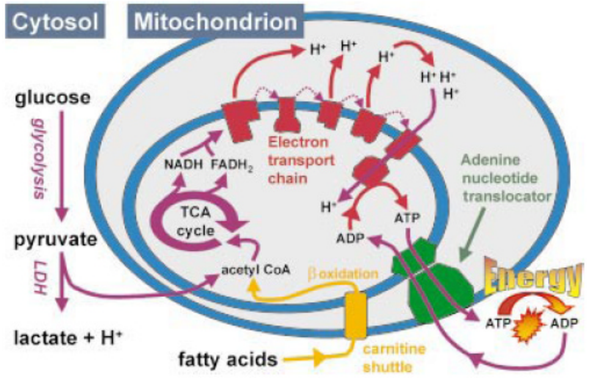
Our patient has a past history of type II diabetes mellitus, essential hypertension and HIV infection and presented with new onset dyspnea at rest, awaking her from sleep. Her symptoms became progressively worse, not relieved by sitting up. She had a mild non-productive cough. She denied chest pain, fever, leg swelling or pain, and she had no nausea, vomiting or hemoptysis. Systematic enquiry revealed watery diarrhea without abdominal cramping for two days. She also commented on weakness and fatigue. She had two previous hospitalizations for community-acquired pneumonia in the past six months. She had a previously negative PPD skin test and her CD4 count was 450 three months before this admission. Her habits involved tobacco smoking, for which she has a 41 pack-year history and quit four months ago. Outpatient medications included a completed course of amoxicillin; gabapentin, amitriptyline, valsartan, metformin, pioglitazone, pravastatin, albuterol MDI, Azmacort inhaler, didanosine, tenofovir and lopinavir/ritonavir. On physical examination, she had a normal mental state, BP 118/62 with a regular pulse of 103 /min, respiratory rate of 18 and temperature of 99°F. She was in mild respiratory distress. Her mucous membranes were pink and moist and her sclera anicteric. Bibasilar rales were heard over both lung bases. Her JVP was not elevated, heart sounds were normal in intensity and there were no audible murmurs. There were no palpable mass or organomegaly on abdominal examination. Extremities were non-edematous and peripheral pulses were normal. Admission ABG on room air pH 7.41, pCO_2 27, pO_2 79, HCO_3 17 and SpO_2 96%. Hb 15 g/dl, Hct 44.7%, WBC 13.9 with 78.3% neutrophils, Platelets 345. BUN 22, Creatinine 0.6, Na 137, K 4.8, Cl 103, serum bicarbonate 24, anion gap 10, glucose 149. Triglycerides 61 mg/dl, AST 27, ALT 22, ALP 77, total bilirubin 0.5. CXR showed scarring consistent with the previous area of pneumonia. EKG showed sinus tachycardia with right axis deviation. The patient was admitted to the medical floor with empiric intravenous ceftriaxone and azithromycin. Metformin was discontinued on admission and lantus insulin prescribed, prophylactic enoxaparin was initiated and all other medications were resumed, including all HAART. Intravenous pentamidine and oral prednisone were started empirically for pneumocystis. Repeat CD4 count was 331 and HIV RNA copies <400/ml. Spiral CT scan of the chest was negative for pulmonary embolus. Perfusion lung scan was low probability for pulmonary embolism.



Action of Didanosine.

Transthoracic echocardiography revealed features of pulmonary hypertension, diastolic dysfunction and normal left ventricular function with no wall motion abnormalities. Bronchoscopy revealed only tracheal candida tropicalis for which intravenous fluconazole was started. All cultures were negative for bacterial growth. Stool studies were positive for clostridium difficile toxin and oral therapy with metronidazole was given. Pentamidine was continued to fourteen days and prednisone tapered. During this time, serum and lipase became modestly elevated (119 U/l and 155 U/dl respectively) but both returned to within normal range after pentamidine was discontinued. Insulin was discontinued because of hypoglycemia. At hospital day 21, three days prior to ICU admission, the patient developed hyperglycemia, and hypotension, the latter was corrected with intravenous fluid bolus. Triglycerides rose to 438 mg/dl and liver transaminases became markedly elevated this time. AST increased from 35 to 100 to 162, ALT increased from 36 to 61 to 126. Total bilirubin increased from 0.7 to 4.6 to 7.1; there was no thrombocytopenia, hemolysis or uremia. When examined by the ICU team, the patient was in severe respiratory distress with aggressive Kussmaul's breathing, tachycardia and a BP of 99/60. On nasal cannula oxygen, ABG performed revealed pH 7.06, pCO_2 13.4, pO_2 138, HCO_3 4 and SpO_2 98%. Serum chemistries at that time: Na 134, K 4.1, Cl 101, serum bicarbonate 6, anion gap 27, glucose 396, acetone 6.6 mg/dl (normal <4.5 mg/dl). The patient was transferred to the medical ICU and all HAART was immediately discontinued. Management for diabetic ketoacidosis began with intravenous insulin and crystalloids, and serum ketonemia and hyperglycemia corrected within six hours. However, acidemia persisted and worsened and the anion gap continued to rise. Serum lactate was measured at 19.4 mm/l. Treatment with l-carnitine and intravenous vitamin B complex was added to her therapy. Aggressive attempts at correcting her acidemia with sodium bicarbonate and fluid resuscitation were unsuccessful. The patient had mechanical respiratory failure requiring intubation and assisted ventilation. Serum lactate increased to 27.4. Cardiovascular collapse ensued requiring vasopressor support, however the patient succumbed to cardiac arrest (the next of kin decided on no resuscitation). The family declined autopsy.

Energy generation in mitochondria



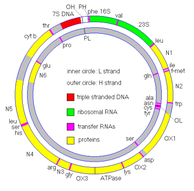
DISCUSSION

A diagnosis of nucleoside reverse transcriptase inhibitor associated lactic acidosis was entertained for this patient. She was maintained on HAART which included two NRTIs (didanosine and tenofovir); metformin was discontinued on admission. Transaminases, bilirubin and triglycerides increased dramatically over a short period of time. A non gap metabolic acidosis was present at admission, but could have been attributable to the mild diarrhea which resolved. There was no identifiable bacterial or pneumocystis infection. Pulmonary embolism was excluded; the pulmonary hypertension may be explained by other causes including HIV itself.

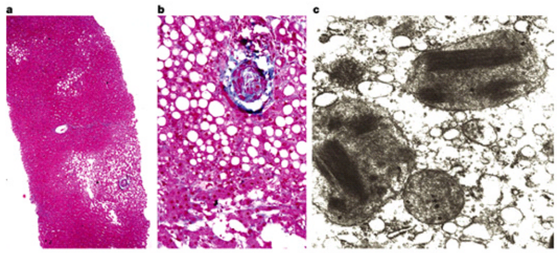
NRTI are used in the treatment of HIV infection as part of HAART regimens, and are efficacious. NRTIs have been shown to inhibit βDNA and γDNA polymerases. βDNA polymerase is involved in the repair of nuclear DNA and its inhibition has not been associated with reportable clinical events to date. γDNA polymerase is associated with the replication of mitochondrial DNA. The main function of mitochondria is to produce energy via oxidative phosphorylation and electron-chain transport. Mitochondrial DNA encodes for some of the enzymes and proteins involved in these intra-mitochondrial metabolic pathways. Pyruvate is the end product of cytosolic oxidative carbohydrate degradation, whereas lactic acid is the anaerobic product from glycolysis. Fatty acids entry into the mitochondria is promoted by l-carnitine and carnitine-palmitoyl transferase. Within the mitochondria pyruvate metabolism and β-oxidation of fatty acids produce acetyl CoA, a substrate for the Kreb's cycle. Dysregulation of these mitochondrial metabolic pathways leads to a decrease in ATP synthesis and an increased NADH/NAD^+ ratio shifting the pyruvate/lactate equilibrium in the direction of lactate. When NRTI toxicity occurs, long chain fatty acids accumulate in the cytosol.

The incidence of lactic acidosis with NRTI therapy is rare, 1.3/1000 to 14.8/1000, varying by definition. Several case controlled studies have tried to define its presentation and risk factors. Clinical signs and symptoms are nonspecific and include nausea and vomiting, abdominal pain, hepatomegaly, asthenia and weight loss, cough and dyspnea/tachypnea, and myalgias in order of decreasing frequency.

Statistically significant risk factors appear to be older age, female gender, presence of diabetes mellitus, recent weight loss, lipodystrophy, stavudine or stavudine-didanosine containing regimen, use of buprenorphine, low creatinine clearance and a low nadir CD4 count. Biochemical features include elevated lactate levels, liver transaminases demonstrating cytolysis and anicteric cholestasis. Other abnormalities may include hypertriglyceridemia, elevated pancreatic enzymes, and increased creatinine phosphokinase and lactate dehydrogenase. Liver pathology almost consistently reveals microvascular, macrovascular or mixed steatosis. Electron microscopy may demonstrate balloonised mitochondria with loss of cristae.



Mitochondrial DNA.



Hepatic steatosis.

Other pathologic findings may include inflammation and necrosis of the pancreas and nonspecific inflammatory edema of the lung.

The outcome of NRTI-induced lactic acidosis is often unfavorable. An attempt has been made to define a threshold blood lactate level that is likely to predict a poor outcome. A value of 9 mmol/l has a positive predictive value of 82%, a negative predictive value of 94.5% and high sensitivity and specificity.

The treatment of these patients involves the immediate interruption of NRTI therapy and maintenance of adequate tissue perfusion. Management of the lactic acidosis should be targeted at the level of ATP production. Supportive therapies including bicarbonate hemodialysis have not been successful. The use of dichloroacetate in the management of lactic acidosis has also had disappointing results. The supplementation of essential cofactors has shown in-vitro success in managing mitochondrial toxicity, however clinical dosage suggestions remain speculative and require randomized clinical trials. The largest report of successful management of NRTI-induced lactic acidosis described survival among six patients with the following regime: vitamin B complex forte (per 2 ml ampoule: 50 mg thiamine, 10 mg riboflavin, 100 mg nicotinamide, 10 mg pyridoxine, 10 mg dexpanthenol) 4 ml twice a day and l-carnitine 1000 mg twice a day, both given intravenously. This treatment is continued until lactate levels fall below 3 mmol/l, after which oral administration might be considered.

CONCLUSION

NRTI toxicity can result in lactic acidosis. The presentation is often non-specific, but possible risk factors, biochemical and pathologic evidence can alert to its development. Outcomes are often not favorable and therefore require early detection, cessation of NRTI therapy and aggressive management.

REFERENCES

F. Bonnet, M. Bonarek, P. Morlat, et al.: Risk Factors for Lactic Acidosis in HIV-Infected Patients Treated with Nucleoside Reverse-Transcriptase Inhibitors: A Case-Control Study. CID 2003; 36:1324–8.

A Arenas-Pinto, A D Grant, S Edwards and I V D Weller: Lactic acidosis in HIV infected patients: a systematic review of published cases. Sex. Transm. Inf. 2003;79:340-343.

Peter W. Stacpoole, PhD, MD, Nelamangala V. Nagaraja, PhD, and Alan D. Hutson, PhD: Efficacy of Dichloroacetate as a Lactate-Lowering Drug. J Clin Pharmacol 2003;43:683-691.

Yann-Erick Claessens, Jean-Daniel Chiche, Jean-Paul Mira and Alain Cariou: Bench-to-bedside review: Severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors. Critical Care 2003, 7:226-232.

Alex J White: Mitochondrial toxicity and HIV therapy. Sex. Transm. Inf. 2001;77:158-173.

Kees Brinkman, Saskia Vrouenraets, Robert Kauffmann, et al.: Treatment of nucleoside reverse transcriptase inhibitor-induced lactic acidosis. AIDS 2000, 14:2801-2802.

Kees Brinkman and Hadewych J.M. ter Hofstede: Mitochondrial Toxicity of Nucleoside Analogue Reverse Trancriptase Inhibitors: Lactic Acidosis, Risk Factors and Therapeutic Options. AIDS Rev 1999; 1: 140-146.

Kees Brinkman, Hadewych J.M. ter Hofstede, et al.: Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS 1998, 12:1735–1744.