Woman with congenital HIV infection and medication-induced Fanconi syndrome

Christian Mabry, MD, Myra A. Kleinpeter, MD, MPH, and D. Luke Glancy, MD

Figure 1. Electrocardiogram recorded soon after admission. See text for explication.

A 19-year-old woman with congenital HIV infection was admitted to the hospital after experiencing nausea, vomiting, diarrhea, and fatigue for 1 week. Her CD4 count was 27. She had undergone percutaneous endoscopic placement of a gastrostomy tube for feeding 5 months earlier. In addition, she had extensive genitoanal ulceration due to infection with herpes simplex virus complicated by secondary bacterial infection. Her home medications included tenofovir disoproxil fumarate, sulfamethoxazole and trimethoprim, lamivudine, lopinavir/ritonavir, duloxetine hydrochloride, Nystatin, azithromycin, hydromorphone, and lorazepam.

An electrocardiogram 11 months earlier had been normal except for sinus tachycardia, but in addition to sinus tachycardia the electrocardiogram recorded soon after the current admission showed changes suggestive of severe hypokalemia (Figure 1):

sagging ST segments, low T waves, and prominent U waves (which because of the tachycardia fuse with the subsequent P waves). Serum electrolyte concentrations in mEq/L were potassium, 1.4; sodium, 139; chloride, 119; and bicarbonate, 14. Her serum calcium concentration was 7.8 mg/dL, and the creatinine and urea nitrogen concentrations were 1.9 mg/dL and 6 mg/dL, respectively. Urinalysis at that time showed a glucose concentration of >1000 mg/dL while her serum glucose was only 90 mg/dL. Her serum uric acid concentration was 0.8 mg/dL, and serum

From the Department of Medicine, Louisiana State University Health Sciences Center (Mabry, Glancy), Tulane University School of Medicine (Kleinpeter), and the Interim LSU Public Hospital.

Corresponding author: D. Luke Glancy, MD, 7300 Lakeshore Drive, #30, New Orleans, Louisiana 70124 (e-mail: dglanc@lsuhsc.edu).

Figure 2. Electrocardiogram recorded shortly before discharge. See text for explanation.

phosphorus was 1.4. The hyperchloremic, hypokalemic, metabolic acidosis was thought to be due to therapy with tenofovir. In addition to this, her metabolic acidosis was certainly exacerbated by recent diarrhea. The tenofovir was discontinued because of the suspected Fanconi syndrome.

After 5 days of aggressive fluid therapy and electrolyte replacement, her serum potassium concentration increased to 4.4 mEq/KL, and the tenofovir was restarted because of her serious HIV infection. After 5 weeks in the hospital, the patient had improved; her electrocardiogram was normal except for sinus tachycardia (*Figure 2*), and she was discharged to inpatient hospice care on numerous medications, including electrolyte replacement.

Six days after discharge, the patient was readmitted with confusion and profound weakness. The admission electrocardiogram, seen in *Figure 3*, showed sinus tachycardia at a rate of 153 beats/minute, right axis deviation, and an intraventricular conduction defect (QRS duration, 0.20 seconds) that suggested hyperkalemia. Serum electrolyte concentrations in mEq/L at this time were potassium, 10.5; sodium, 135; chloride, 120; and bicarbonate, 12. The serum calcium level was 14.5 mg/dL despite a serum albumin level of only 2.2 gm/dL, the highest albumin level recorded during either admission. Her serum creatinine and urea nitrogen concentrations were 2.5 mg/dL and 41 mg/dL, respectively. As the hyperkalemia was treated with oral sodium polystyrene sulfonate, insulin, 50% dextrose solution, and emergent hemodialysis, the QRS duration shortened to 0.12 seconds, and T waves became more peaked and “typical” of hyperkalemia (*Figure 4*). In addition, the QT interval was noticeably short considering the intraventricular conduction defect

(QT interval, 0.25 seconds; QT interval corrected for heart rate, 0.40 seconds), a feature consistent with hypercalcemia.

One of the patient’s discharge medications on her previous admission was potassium chloride, 60 mEq three times per day by mouth, and that dosage in the presence of her renal dysfunction undoubtedly caused the hyperkalemia that occasioned the second admission. She improved, but never sufficiently to leave the hospital. Her stay was complicated by multiple nosocomial infections, pressure sores, and worsened debilitation, and she eventually developed gram-negative sepsis and died 6 weeks after admission.

DISCUSSION

Vertical transmission of HIV continues to be a serious health problem in developing countries, with over 95% of congenital HIV occurring in these areas (1). Most of these infected neonates acquire the virus either during or near the time of delivery (2). The widespread use of highly active antiretroviral therapy has decreased this transmission rate from 25% (no treatment) to 2%, and this rate can be further decreased to <1% if prophylactic cesarean section is performed in mothers with viral loads >1000 (2). The potential complications of highly active antiretroviral therapy should never outweigh the benefits of starting this treatment as soon as the infection is found. Data from 2004 showed a 95% decrease in cases of perinatally acquired immune deficiency syndrome when the appropriate treatment and preventative measures were taken (2). Clinicians must always be conscious of the potential complications, however, as they may occur at any time during treatment and can have devastating consequences.

Figure 3. Electrocardiogram recorded on the second admission. See text for explication.

Figure 4. Electrocardiogram recorded an hour after the electrocardiogram in Figure 3. See text for explication.

The first antiretroviral to be approved to prevent perinatal HIV transmission was zidovudine in the mid 1990s (2). Since that time, many different drugs have been developed, which have successfully reduced transmission to its present rate (2).

The use of up to four medications in combination allows for the viral replication cycle to be interrupted at multiple steps (2). Tenofovir is a nucleotide reverse transcriptase inhibitor that prevents replication of the virus by competing for incorporation

into its DNA (3). The drug's synergistic actions with other HIV medications make it perfect for use in a multidrug regimen.

Complications of tenofovir therapy include lactic acidosis, Fanconi syndrome, immune reconstitution syndrome, severe acute exacerbation of hepatitis, decreases in bone mineral density, and severe hepatomegaly with steatosis. Fanconi syndrome, a known complication of tenofovir, has occurred in about 1.6% of patients who used the drug and has been characterized by the passage of glucose, amino acids, uric acid, phosphate, and bicarbonate in the urine instead of their being reabsorbed (4). Because of the low incidence of this side effect, it was not widely recognized until tenofovir was used in large populations (3).

The nephrotoxicity of tenofovir is due to mitochondrial dysfunction. This causes a significant decrease in the energy for the sodium-potassium pump in the proximal tubules (3). This disruption allows for electrolytes and small molecules that would normally be reabsorbed to be lost in the urine (3). As Fine described, "The result is a proximal renal tubular acidosis (usually hypokalemic) with hypophosphatemia, glucosuria, and aminoaciduria (Fanconi syndrome)" (3). Not all of these laboratory abnormalities will be present in every case; many times, the kidneys will compensate and only one or two of these disturbances will be seen (3). Risk factors for tenofovir-associated nephrotoxicity include preexisting kidney disease or elevated creatinine, poorly controlled HIV disease with overall antiretroviral treatment duration, CD4 nadir <200 cells/mm³, African American ethnicity, older age, female gender, and concomitant administration of nephrotoxic agents (5, 6).

Virtually no computer program attempts to read the electrocardiographic changes of electrolyte disturbances. Thus, physicians must recognize these changes on their own. Serum potassium disturbances produce some of the most striking findings. Hypokalemia is characterized by sagging ST segments, low T waves, and prominent U waves (7). One or more of these features may be seen with a serum potassium of 3.0 to 3.5 mEq/L, and below 2.5 mEq/L all three features are usually present (8). With strikingly low levels of serum potassium (Figure 1), the T wave becomes a notch on the upslope of a giant U wave and may fuse with the U, giving the impression of a long QT interval. In the presence of ST-segment depression, the changes may be mistaken for those of ischemia (7). Peaked T waves may be present when the serum potassium rises above 5.5 mEq/L and are present in most patients with levels above 6.7 mEq/L (8). As

the potassium rises above 8 mEq/L, the QRS widens diffusely and only rarely resembles typical right or left bundle branch block (Figure 3). The PR interval may lengthen, and the P waves become less distinct and may disappear. Ventricular asystole or fibrillation often occurs when the serum potassium exceeds 12 mEq/L (8). The QTc interval is inversely proportional to the level of the ionized serum calcium (8), and it is the ST segment rather than the T wave that is altered (9). Thus, hypercalcemia causes shortening or virtual disappearance of the ST segment (Figure 4), whereas hypocalcemia causes QTc prolongation by lengthening the ST segment.

In our patient, electrocardiographic changes resulted from multiple electrolyte abnormalities that were corrected during the initial hospitalization. The overcorrection on an outpatient basis was further accentuated by the development of acute renal failure, and tenofovir therapy contributed to it in a debilitated patient with chronic infection. Tenofovir may be used safely in high-risk patients, but close monitoring is necessary to prevent electrolyte abnormalities that may be manifested by life-threatening electrocardiographic changes.

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