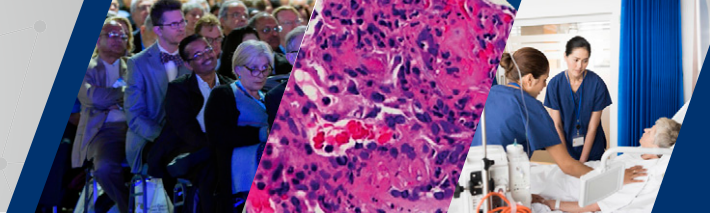

Management Consideration in Drug-Induced Lactic Acidosis

Alexander Morales and *John Danziger*

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Division of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Correspondence: Dr. John Danziger, Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, 171 Pilgrim Road, Libby 2, Boston, MA 02215. Email: jdanzige@bidmc.harvard.edu

Although a litany of pharmacotherapeutic agents has been implicated in drug-induced lactic acidosis, the expanding use of nucleoside/nucleotide reverse transcription inhibitors (NRTIs) makes this class of drugs increasingly important for nephrology awareness. Once used primarily in HIV treatment, NRTIs are now used for management of hepatitis B infection and primary HIV pre-exposure prophylaxis, and they are likely to be increasingly encountered as a cause of lactic acidosis.

Consider the case of a 76-year-old woman with a history of congestive heart failure, type 2 diabetes, and HIV on an antiretroviral regimen of bictegravir, emtricitabine, and tenofovir alafenamide. She presented with increasing confusion and tachycardia from a skilled nursing facility. On presentation, the patient was afebrile and normotensive with mild tachycardia to 105 bpm; her weight was 72 kg. Initial laboratory studies were notable for a creatinine of 1.6 mg/dl, bicarbonate of 22 meq/L, anion gap of 22, alanine aminotransferase of 110 IU/L, aspartate aminotransferase of 142 IU/L, and total bilirubin of 2.4 mg/dl. Chest radiography disclosed a small right lower-lobe consolidation and mild pulmonary edema, raising concern for pneumonia and exacerbation of congestive heart failure. She was admitted to the general medicine ward for intravenous antibiotics and diuretics.

Approximately 12 hours after admission, the patient became increasingly confused, at which time repeat laboratory studies revealed further elevation of liver transaminases, creatinine of 2.0 mg/dl, bicarbonate of 9 meq/L, anion gap of 35, venous pH of 7.16, and serum lactate of 14 mmol/L. She was transferred to the intensive care unit, where she developed hemodynamic compromise and worsening oliguria. Given that she was afebrile with a normal white blood cell count, normal abdominal examination and imaging, and negative blood and urine cultures, drug-induced lactic acidosis was considered high on the differential. Nephrology was consulted for the management of acute lactic acidosis and specific consideration of KRT.

The mechanism of NRTI-associated lactic acidosis is presumably through direct mitochondrial toxicity, interfering with the Krebs cycle and electron transport chain and, thereby, disrupting cellular oxidative metabolism and shifting toward anaerobic metabolism. Although asymptomatic, low levels of lactic acid production occur in approximately 15% of NRTI users (1) and are typically metabolized by the liver and kidney. Under certain circumstances, however, production can overwhelm the metabolic compensatory mechanisms, causing life-threatening acidosis. Because tenofivir is also known to impair proximal tubule function, thereby impairing the compensatory lactate metabolism in the kidneys, it is a particularly worrisome cause of drug-induced lactic acidosis (2,3).

Although the management of lactic acidosis is a cardinal therapeutic goal of NRTI toxicity, specific guidelines have not yet been developed. Extrapolation from the Extracorporeal Treatments in Poisoning workgroup's guidelines on KRT in metformin toxicity suggests extracorporeal therapy when serum lactate is >20 mmol/L, when blood pH is ≤7.0, and if standard therapy, including bicarbonate administration, fails (4). Although our patient did not meet any of the criteria for immediate KRT, there were worrisome aspects in her decline. In considering the management of drug-induced lactic acidosis, we feel that predicting the trajectory of acidosis is important in determining if the risks of KRT initiation are warranted (Figure 1).

The known drug $t_{1/2}$ and dialyzability of the offending agent affect the duration of continued mitochondrial dysfunction and expected lactate production. Although metformin's plasma $t_{1/2}$ is approximately 6 hours, tenofovir alafenamide has a short serum but prolonged intracellular $t_{1/2}$ and high volume of distribution (5). The $t_{1/2}$ of both agents may be further prolonged in the setting of kidney insufficiency. Although metformin is thought to be reasonably dialyzable, with a hemodialysis clearance of 200 ml/min, tenofivir's dialytic clearance is considerably less (estimated at 130 ml/min) (3).

Given our patient's concomitant use of tenofivir alafenamide and underlying hepatic and kidney injury, a predictable trajectory of lactic acid production and inadequate metabolic compensatory mechanisms increased her risk for severe acidosis and underscored the need for vigorous bicarbonate supplementation.

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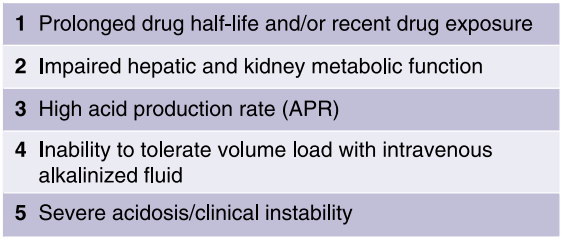

Figure 1. | Factors favoring KRT for management of drug-induced lactic acidosis.

In order to determine how much and how quickly bicarbonate supplementation would be needed, we approximated the acid production rate. The acid production rate mirrors the bicarbonate consumption over time, and it can be simply estimated: acid production rate = change in serum bicarbonate over any time period (in hours) $\times 0.4 \times$ body weight (in kilograms).

Given that our patient's bicarbonate decreased from 22 to 9 meq/L over a 12-hour period, her acid production rate was 374 meq of H^+ equivalent over 12 hours or 31 meq H^+/h. We considered replacing this bicarbonate consumption as a primary therapeutic goal.

Although three ampules of $NaHCO_3$ in 1 L of dextrose 5% in water (D5W) delivers 150 meq of bicarbonate, given our patient's oligoanuric AKI, development of hypotension, and concomitant pulmonary edema, we thought dialysis would be the safer method of bicarbonate supplementation. Despite lower hourly dialytic clearance of continuous KRT than conventional hemodialysis, its continuous nature allows robust bicarbonate delivery, with the additional benefit of close titration according to changes in the acid production rate. Although the ratio of pre- and postfilter replacement might minimally affect the efficiency of bicarbonate delivery, the amount can be simply estimated with the following formula: estimated continuous RRT (CRRT) bicarbonate delivery per hour = (CRRT fluid bicarbonate – serum bicarbonate) $\times$ total CRRT fluid volume in liters (replacement and dialysate).

Accordingly, given our patient's bicarbonate concentration of 9 meq/L, a standard CRRT bicarbonate solution of 32 meq/L would deliver 23 meq of bicarbonate per liter of dialysate/replacement fluid using continuous venovenous hemodiafiltration. We chose a replacement fluid rate of 4 L/h and a dialysate rate of 2 L/h in order to provide 138 meq/h of bicarbonate, with the plan of titrating CRRT volumes down as the bicarbonate level normalized.

Although such empirical calculations remain somewhat crude, they allow an estimation of the trajectory of acid production and guide treatment. Presently, there are no data from randomized controlled trials suggesting an appropriate dosage strategy as it pertains to CRRT and management of drug-induced lactic acidosis. Importantly, our calculation is likely to overestimate the amount of delivered bicarbonate given that the patient's serum bicarbonate will improve over time. The volume of delivered bicarbonate can only be truly ascertained when correction of the acidosis has been completed and the required duration of the effort is known. In accordance with this notion, frequent monitoring of serum chemistries and blood gas analysis are paramount for appropriate titration of CRRT fluid volumes. In our case, it took longer than the 2–3 hours predicted for the serum bicarbonate to normalize, possibly reflecting a higher than estimated acid production rate with endogenous bicarbonate consumption. Eventually, after approximately 10 hours, her serum bicarbonate reached 22 meq/L, and her CRRT volumes were accordingly decreased. At that point, because each liter of CRRT would provide 10 meq/L of bicarbonate, her dialysate and replacement fluid rates were reduced to 1.5 L/h (total of 3 L/h) to provide enough bicarbonate to match her acid production rate.

Within 48 hours, the lactate levels began to fall, and CRRT was discontinued. Her liver enzymes improved, and creatinine returned to a near baseline of 1.2 mg/dl. She was discharged from the intensive care unit and eventually returned home.

In summary, drug-induced lactic acidosis may be severe and is associated with a high morbidity and mortality. Known $t_{1/2}$ and kidney pharmacokinetics of the suspected offending agent may predict the durability of lactate production, and KRT should be considered in the setting of kidney insufficiency, concomitant liver injury, and a high acid production rate.

Disclosures

All authors have nothing to disclose.

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