Rapid Onset of Fatal Lactic Acidosis Complicating Tenofovir Therapy in a Diabetic Patient with Cirrhosis: A Cautionary Tale

Sir,

A nucleotide analogue (NA) has potential to cause mitochondrial (mt) toxicity which may lead to the development of lactic acidosis (LA).¹ Tenofovir, a nucleotide analogue, induced LA is extremely rare because of its low affinity for mt DNA polymerase.² We report a 45-year-old gentleman, with a background history of diabetes mellitus (DM) and hepatitis B virus related liver cirrhosis, who developed fatal LA after initiation of tenofovir. The patient had advanced cirrhosis with Model for End-stage Liver Disease score of 24, and he had not been on any anti-diabetic medication for 3 months. Only a week after initiation of tenofovir, he was brought to emergency with 1-day history of pain abdomen, breathlessness, generalized weakness, decreased consciousness, and left lower limb cellulitis. His laboratory tests were as follows: serum bilirubin 4.1 mg/dl, alanin transaminase: 103 IU/L, aspartate transaminase 115 IU/L, serum albumin 2.6 g/dl, white blood cell count 10,240/mm³, blood urea 50 mg/dl, serum creatinine 1.0 mg/dl, and international normalized ratio 3.09. His arterial blood gas (ABG) revealed pH of 7.35, HCO₃⁻ of 11 mmol/L, and lactate level of 9.8 mmol/L. Within few hours after admission his condition deteriorated further, and his repeat ABG revealed metabolic acidosis (pH 7.20, HCO₃ 11.8) with increasingly level of lactate (11.2 mmol/L). The patient was managed with intensive supportive treatment. His tenofovir was discontinued. However, his LA further worsened (level 15.8 mmol/L), and he developed progressive multi-organ dysfunctions. Despite all measured he succumbed to his illness, after 3 days of admission.

It is estimated that 8–21% of NA-treated patients have hyperlactatemia, while 1–2% develop severe LA.³ LA is caused by lactate overproduction or underutilization.⁴ Approximately 1400 mmol of lactic acid are produced daily, however, the lactate concentration in plasma remains below 1 mmol/L because of efficient lactate clearance by liver. It is not clear as to why tenofovir induced LA occurs only rarely. The mt DNA polymorphism, depletion of exogenous factors involved in mitochondrial oxidative phosphorylation (e.g., riboflavin

and thiamine), synergistic effects of concomitant medications, and sepsis may explain this.⁵ Furthermore, diabetic patients are more prone to develop LA.⁶ Although the development of LA has been reported to occur only after weeks to months of exposure, it can be accelerated if multiple predispositions are present.⁵ The mortality rate amongst patients with LA induced by NAs other than tenofovir is high, ranging from 33% to 57%.⁷ One may question as to whether tenofovir was an innocent bystander in the present case. Though it is difficult to establish that tenofovir was the sole culprit, multiple factors (liver dysfunction, sepsis, individual susceptibility, etc.) might have played a role in the development of severe LA. At presentation, there was no florid sepsis, hypoperfusion state or concomitant medication (such as metformin or other NAs) that could cause severe hyperlactatemia. The only change that had happened of late was an addition of tenofovir, and given its potential to cause hyperlactatemia, its role cannot be disregarded either. To date, we do not have a prospective study where serial measurement of blood lactate has been done in cirrhotic patients after initiation of tenofovir. When there is pre-existing risk factors for lactate overproduction (sepsis) and lactate under clearance (advanced cirrhosis), even minor degree of hyperlactatemia produced by another source would be added up leading to severe hyperlactatemia and hence LA. Therefore, the safety of tenofovir must be assessed prospectively in patients with advanced cirrhosis and sepsis

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