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Fanconi Syndrome Due to Tenofovir Disoproxil Fumarate in a Patient with Chronic Hepatitis B Induced Cirrhosis: A Case Report

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ABSTRACT

We present a 63-year-old woman with chronic hepatitis B. The patient has a history of cirrhosis due to chronic hepatitis B and is under treatment with Tenofovir disoproxil fumarate. The patient presented to our center with nausea, vomiting, and severe metabolic acidosis. After initial evaluation, along with the typical course of events and the exclusion of differential diagnoses of normal anion gap metabolic acidosis, we determined that the cause of illness was related to Tenofovir disoproxil fumarate. All our practical and laboratory data supported a diagnosis of proximal tubular acidosis. After discontinuing the drug for two weeks and providing supportive management, metabolic acidosis and electrolyte imbalance improved. The other isoform of Tenofovir (Tenofovir alafenamide) was initiated for the patient, and after two months of follow-up, there were no signs of acidosis or electrolyte imbalance.

Introduction

Chronic Hepatitis B is one of the causes of cirrhosis; we will present a case with hepatitis B-induced cirrhosis. Several therapeutic agents are used against hepatitis B. Nucleotide analogs are one of these drugs that are administered orally. There are two main prodrugs of tenofovir, as described below.

Tenofovir disoproxil fumarate is licensed for use in children older than 2 years with chronic hepatitis B [1]. Safety considerations include renal toxicity and reduction in bone density.

Tenofovir alafenamide is licensed for use in individuals aged 12 years and older with chronic hepatitis B [2]. It appears to have less renal and bone toxicity than tenofovir disoproxil fumarate.

Case presentation

A 63-year-old woman presented to our hospital center with complaints of nausea and vomiting for 10 days before admission. The vomiting was nonbilious and non-bloody. The patient also suffered from low back pain and notable weight loss over the past six months.

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Other accompanying symptoms included constipation without any signs suggestive of gastrointestinal obstruction. It's also worth mentioning that the patient was diagnosed with diabetes mellitus around four years ago and had cirrhosis of the liver due to chronic Hepatitis B infection.

For Hepatitis B, she is under antiretroviral therapy with Tenofovir disoproxil fumarate 300 mg daily. Regarding her medical history, she had one episode of ascites six months ago, during which the fluid was drained, and pathology samples were sent. Fortunately, no evidence of malignant cells was found.

In a previous hospitalization at another center, an upper GI evaluation with esophagogastroduodenoscopy revealed erosive gastropathy and snaked skin pattern gastritis. In the primary investigation at our center, she had uncontrolled blood sugar levels with severe metabolic acidosis, leading to a high suspicion of diabetic ketoacidosis. Further evaluation revealed a normal anion gap metabolic acidosis, hypokalemia, and a urine pH of 5.

In further evaluation, laboratory findings revealed a normal anion gap metabolic acidosis, hypokalemia, and a urine pH of 5.

Primary and follow-up Laboratory tests

Urine Analysis:

Color: Yellow

Appearance: Semi-Turbid

PH: 5

Protein: 1+

Glucose: 3+

Ketone: Negative

Blood: Negative

RBC: 1_2

WBC: 0_1

Epithelial cell: 0_1

Cast: Negative

Crystal: Negative

Bacteria: Negative

Yeast: Negative

According to the laboratory tests above, we approached the underlying condition causing severe metabolic acidosis. The anion gap calculation equals 11. The differential diagnosis for normal anion gap metabolic acidosis consists of two significant etiologies: diarrhea and renal tubular acidosis. As

Primary laboratory tets		Two months later
WBC	6000 cells / micL	4000 cells/micL
Hb	14.6 g/dL	13.7g/dL
MCV	94 fL	
PLT	132000/ micL	71000/micL
PH	7.129	7.38
PCO2	*31.7*	44.6
HCO3	10.5	24.4
Na	133mEq/L	142mEq/L
K	2.5mEq/L	4.9 mEq /L
Cl	122mEq/L	110 mEq /L
BUN		16 mg/dl
Cr	28 mg/dl	1.2 mg/dl
Mg	2.3 mg/dl	
	1.4 mg/dl	2 mg/dl
Uric acid	2.3 mg/dl	
	9.8 mg/dl	3 mg/dl
Ca	2.8 g/dl	
		8.3 mg/dl
Albumin		
ESR	7	
CRP	11	
Alfa FP	9.97 (0.89_8.78)	

mentioned in the history, the patient suffered from constipation during the days before admission. Given the renal impairment and after evaluating prerenal and postrenal causes of renal injury, we expected high concentrations of uric acid, magnesium, and phosphorus in the bloodstream; unexpectedly, the serum levels of uric acid, magnesium, and phosphorus were low.

Clinical and laboratory data were highly suggestive of proximal tubular acidosis (Fanconi syndrome). Significant causes of acquired proximal renal tubular acidosis include Sjögren syndrome, vitamin D deficiency, heavy metal poisoning, M protein disorders such as multiple myeloma, and drug-induced renal tubular acidosis. There was no history of symptoms or clinical features in favor of Sjögren syndrome; multiple myeloma could be ruled out due to a normal erythrocyte sedimentation rate and normal hemoglobin levels, and there was no history of exposure to materials containing heavy metals. On the second day of hospitalization, the diagnosis of drug-induced proximal renal tubular acidosis was made. Tenofovir disoproxil fumarate was discontinued, and initial treatment for electrolyte imbalance and acidosis correction began.

The patient was given potassium citrate, phosphate supplements, and sodium bicarbonate. Soon after, the patient improved, and the oral intolerance was resolved. After discharge and follow-up, metabolic acidosis subsided. Although Tenofovir is a known cause of drug-induced proximal RTA, in our clinical setting, we decided to initiate another isoform of antiretroviral drugs for the patient; one of these drugs indicated for this patient is Tenofovir alafenamide. Subsequent follow-up will help compare these two antiretroviral drugs and determine if there is a similar potency to cause tubulopathy.

Discussion

Two main organs contribute to the body's acid-base balance and do so with complex mechanisms. Among disorders that cause a normal anion gap metabolic acidosis accompanied by potassium imbalance are two types of renal tubular acidosis. Type 1, or distal renal tubular acidosis, and Type 2, or proximal renal tubular acidosis, are two primary forms of tubulopathies that cause acid-base imbalance.

These are mainly pediatric diseases and genetic disorders and are not commonly diagnosed in adulthood. A brief review of the kidney's pathophysiology and acid-base balance function will help us further understand the mechanisms behind renal tubular acidosis. Tubular cells in the proximal convoluted tubule have two surfaces: the apical (luminal) surface and the basolateral surface. On the apical surface of proximal convoluted tubules, bicarbonate that filtrates in the glomerulus is reabsorbed into the blood via counter-transport of sodium and hydrogen. If the capacity for bicarbonate reabsorption is impaired, Type 2 or proximal tubular acidosis will occur.

Proximal tubular acidosis can be isolated or occur with other solute reabsorption impairments such as glucose, amino acids, phosphorus, and uric acid. In adults, proximal tubular acidosis may occur due to M protein disorders such as multiple myeloma and other monoclonal gammopathies [3]. These disorders represent the toxic effects of immunoglobulin light chains on kidney tubular cells [4,5].

Some drugs are also known for causing proximal tubular acidosis. Topiramate and acetazolamide, through carbonic anhydrase enzyme inhibition, can cause renal tubular acidosis [6]. Nephrotoxic drugs like ifosfamide and tenofovir, as well as inflammatory diseases such as Sjögren's syndrome, are other etiologies of renal tubular acidosis [7-9].

As mentioned above, we discontinued Tenofovir disoproxil fumarate for two weeks, and after this, the patient was initiated on 25 mg of Tenofovir alafenamide daily. Clinical symptoms improved after two months of follow-up, and metabolic acidosis and electrolyte imbalance completely resolved.

Conclusion

It seems that periodic monitoring in selected patients under treatment with Tenofovir is necessary and plays a vital role in distinguishing its practical impacts on kidney function. Simple and cost-effective laboratory tests should be considered for this purpose. The monitoring interval is a challenging issue that could be evaluated in subsequent studies.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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