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Tenofovir Therapy Induced Fanconi Syndrome: A Rare Complication In Hepatitis-B Virus Infected Patient.

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ABSTRACT

Fanconi syndrome is very uncommon in hepatitis B virus infected patients treated with tenofovir. Proximal tubular cells of kidney are particularly sensitive to the toxic effects of tenofovir due to their unique set of cell membrane transporters that favour entry of the drug. A 47-year old male with hepatitis-B virus (HBV) infection presented with sudden onset of weakness of all four limbs, difficulty in walking, myalgia and slurring of speech, polyuriasince past two days. Twelve months before admission, the patient had been initiated on tenofovir 300 mg as treatment for HBV infection.Fanconi syndrome (FS) was diagnosed based on normal anion gap acidosis with hypokalemia, hypophosphatemia, glucosuria, aminoaciduria (Amino acid presence in urine- very high), and proteinuria. This case and the other cases reported to date suggest thattenofovir causes Fanconi syndrome, and that this may become more problematic with more widespread use of the drug. The possibility of irreversible renal damage also suggests that patients given this drug should be followed more closely in the 12- to 18-month period after initiation of tenofovir therapy and should have a urinalysis, serum creatinine, and potassium performed on a regular basis following initiation of therapy. Raising the awareness of clinicians with regard to the potential for this side effect is important so that patients with this side effect can be discovered early and switched to an alternate antiviral therapy.

Keywords: Fanconi syndrome, Tenofovir, HBV, Tubular injury

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INTRODUCTION

More than 350 million people worldwide are chronically infected with hepatitis B virus (HBV). Complications of chronic hepatitis B, such as cirrhosis, hepatocellular carcinoma, and end-stage liver disease, account for approximately one million deaths each year [1]

Tenofovir disoproxil fumarate is an orally bioavailable prodrug of tenofovir, an acyclic nucleotide analogue reverse transcriptase inhibitor (NtRTI) structurally similar to adefovir and cidofovir [2]. Acyclic nucleotides differ in their side chains: hydroxyl phosphonomethoxypropyl (HPMP) for cidofovir, phosphonomethoxyethyl (PME) foradefovir and phosphonomethoxypropyl (PMP) for tenofovir [3]. Tenofovir diphosphate is a structural analog of deoxyadenosine-5′-triphosphate, the usual substrate for viral RNA-directed DNA polymerase, and is a weak inhibitor of mammalian DNA α- and β-polymerases and mitochondrial DNA γ-polymerase [4]. Tenofovir was the first (2001), and remains the only, nucleotide reverse transcriptase inhibitor (NtRTI) approved by the US Food and Drug Administration (FDA) for the treatment of HIV infection [2]. Tenofovir was also approved for treatment of chronic hepatitis B in adults in 2008 [5]. Tenofovir is eliminated unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion [6]. 20–30% of the drug is actively transported into renal proximal tubule cells by organic anion transporters (hOAT1, and to a lesser extent, OAT3) in the basolateral membrane [7, 8]. Subsequently the drug is secreted to the tubular lumen by the apical membrane transporters MRP-4 and MRP-2 (multidrug resistance proteins, encoded byABCC4 and ABCC2 genes) [9]. A large numberof drugs interact with these transporters and may cause excessive entry or reduced outflow of the drug, favouring intracellular accumulation and increasing renal toxicity. Despite initial cell culture and clinical trials results supporting the renal safety of tenofovir, its clinical use is associated with a low, albeit significant, risk of kidney injury. Proximal tubular cell secretion of tenofovir explains the accumulation of the drug in these mitochondria rich cells. Tenofovir nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease [10]. Here, we report a new case of renal tubular injury in HBV infected patient treated with tenofovir.

Case Report

A 47-year-old male with hepatitis-B virus (HBV) infection presented with sudden onset of weakness of all four limbs, difficulty in walking, myalgia and slurring of speech for the last two days. He also noted polyuria for the last two days. Twelve months before admission, the patient had been initiated on tenofovir 300 mg as treatment for HBV infection.

Patient is a known type II diabetes mellitus and hypertension for the last 10 years and is treated with Tablet glimepiride 2 mg, Tablet voglibose 0.3 mg and Tablet amlodipine 5 mg. No other central nervous system symptoms. No history of vomiting, hematemesis, abdominal pain, loose stools or fever. He was not an alcoholic or tobacco user. There was no known family history of neurological disease or renal disorders.

Physical examination revealed that he was moderately built and nourished. There was no acute respiratory distress. His body temperature was 37°C, blood pressure 180/80 mmHg, and heart rate 68 beats per minute. Dysarthria was present. He had decreased muscle strength (3/4) bilaterally with normal and symmetrical reflexes. Sensory examination was normal. There was pure motor quadriplegia with preserved reflexes.

At admission in the ward, his serum potassium was 2.0 meq/L, serum glucose 136 mg/dL, serum sodium 143 meq/L, serum chloride 126 meq/L, and serum bicarbonate 19 meq/L. An arterial blood gas (ABG) test showed severe metabolic acidosis with an anion gap of 7.8 demonstrating a normochloremic anion gap metabolic acidosis. Serum albumin was 5.1 mg/dL and serum phosphorus was markedly low at 0.5 mg/dL. Other laboratory values of note at admit are as follows: urine sodium 35 meq/L, urine potassium 19.9 meq/L, and urine creatinine 2.5 meq/L (urine anion gap 12), with a fractional excretion of sodium 4.1%. A urine analysis showed a urine pH of 5.5, 100 mg/dL of protein, and glucose 136 mg/dL.

Fanconi syndrome (FS) was diagnosed based on normal anion gap acidosis with hypokalemia, hypophosphatemia, glucosuria, aminoaciduria (Amino acidpresence in urine- very high), and proteinuria. Suspecting that FS was due to tenofovir, it was stopped. The patient was aggressively rehydrated with

intravenous fluids. He required replacement with 100 mEq potassium chloride twice daily for 2 days to keep potassium above 3 mEq/L for the first 5 days of hospitalization. Phosphorus was also replaced orally. The patient's condition improved dramatically within 24 hours of hospitalization, with normalization of his creatinine. The patient's renal function also improved during hospitalization, and upon discharge on hospital day #8 his creatinine level had stabilized at 1.4mg/dL.

DISCUSSION

Fanconi's syndrome was first described by Lignac in 1924 and further defined by Fanconi in 1936 in children presenting with rickets, growth retardation, and glucosuria. Heritable FS is transmitted as an autosomal recessive trait and occurs in 1 in40,000 births [11]. This is characterized by a generalized defect in proximal tubular function with subsequent aminoaciduria, glucosuria with normal serum glucose, and phosphate wasting [12]. On a cellular level, it has been proposed that disruption of the Na+-K+-ATPase pump on the basolateral membrane of the proximal tubular cell could inhibit active transport into the peritubular capillaries. Another theory is that active transport may remain intact but the permeability of the proximal tubule is increased, thereby significantly enhancing back-diffusion of solutes [12]. In the case presented in this article, the most likely factor causing the patient's FS was a drug. A search of the literature reveals that several drugs apart from tenofovir have been implicated in causing FS, among them aminoglycosides, ifosfamide, cisplatin, streptozocin, mercaptopurine, tetracycline, and valproic acid [13]. Most importantly, for this case, certain anti-retrovirals have been implicated in causing FS, namely cidofovir, adefovir [12] and 1 case of didanosine [14]. However, it is important to note that the focus of this article is to highlight the unique association of FS with tenofovir. Our patient had been taking tenofovir for about 12 months before presentation. A close review of his serum potassium and creatinine shows evolving hypokalaemia and declining renal function during this period. With the discontinuation of tenofovir, his metabolic abnormalities gradually resolved.

Concerns regarding nephrotoxicity were initially raised by the structural similarity between tenofovir and the nephrotoxic acyclic nucleotide analogues adefovir and cidofovir. Tenofovir is extensively excreted by the renal route by means of glomerular filtration and active tubular secretion [15].This drug is structurally close to adefovir and cidofovir, which are used in the treatment of hepatitis B infection and cytomegalovirus infection, respectively [16,17]. High doses of adefovir and cidofovir have been involved in renal injuries [18].Moreover, 2 cases of Fanconi syndrome have been previously reported with cidofovir [19,20].

This case and the other cases reported to date suggest that tenofovir causes FS, and that this may become more problematic with more widespread use of tenofovir. Proximal tubular cells are particularly sensitive to the toxic effects of tenofovir due to their unique set of cell membrane transporters that favour entry of the drug. In this regard, the design of novel, less cytotoxic drugs is centred on chemical modifications that limit entry into proximal cells. The possibility of irreversible renal damage also suggests that patients given this drug should be followed more closely in the 12- to 18-monthperiod after initiation of tenofovir therapy and should have aurinalysis, serum creatinine, and potassium performed on a regular basis following initiation of therapy. Raising the awareness of clinicians with regard to the potential for this side effect is important so that patients with this side effect can be discovered early and switched to an alternate antiretroviral therapy.

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