CASE REPORT

Acquired Fanconi's Syndrome Associated with Tenofovir Therapy

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Tenofovir (Viread®) is a nucleotide reverse transcriptase inhibitor introduced into the United States in 2001. It is frequently prescribed not only for its efficacy but also for its decreased side effect profile compared with other nucleoside analogs. It is now increasingly recognized as a cause of acquired Fanconi's syndrome (FS) in human immunodeficient individuals. We describe a case of a patient with AIDS, who, after starting tenofovir therapy, developed myalgias, renal failure, and profound electrolyte abnormalities compatible with the classic features of FS. On discontinuation of tenofovir and replacement of electrolytes, the individual improved clinically with normalization of his renal failure and electrolyte abnormalities. With the success of tenofovir in the anti-HIV drug market, practitioners should remain alert to the possibility of the development of FS. Frequent urine, renal, and electrolyte parameters should be measured at regular intervals following initiation of tenofovir therapy.

KEY WORDS: Fanconi's syndrome; tenofovir; renal tubular acidosis; HIV.

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Tenofovir has emerged as an important member of antiretroviral therapy since its introduction in 2001. In addition, it is now a key component of Truvada® (Gilead Sciences, Foster City, CA), which is a co-formulation of tenofovir and emtricitabine. Ongoing efforts are now focused on adding efavirenz to create a once-a-day pill.

In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5' monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase. It is primarily excreted through the kidney via glomerular filtration and active tubular secretion. Nephrotoxicity owing to tenofovir has been reported in the literature over the past few years.[1–7]

A case of Fanconi's syndrome (FS) is reported here in an AIDS patient taking tenofovir. Our case and others reported to date suggest that patients taking tenofovir should be monitored frequently with urinalysis and serum renal panels at least for 18 months after initiation of therapy.

CASE SUMMARY

A 38-year-old male with AIDS presented with a 3-day history of muscle weakness and myalgias beginning in his lower extremities and spreading proximally to his trunk and upper extremities. He also noted increasing fatigue and polyuria over the past 3 days. Six months before admission, the patient had been initiated on tenofovir, lamivudine, and efavirenz. He responded well to this new antiretroviral regimen both virologically and immunogically as his CD4 count rose from 37 to 287, and an undetectable viral load was noted just 2 weeks before this admission.

Besides a history of HIV detected 9 years back, the patient's medical history was significant for severe peripheral neuropathy secondary to HIV, gastro esophageal reflux disease, and epilepsy. He denied any alcohol, tobacco, glue sniffing, or illicit drug use.

He reported no history of diarrhea. There was no known family history of neurological disease or renal disorders. The patient had no known medication allergies.

Physical examination revealed a cachetic, anxious patient in no acute respiratory distress. His admission temperature was 37 °C, blood pressure 110/80 mmHg, and heart rate 80 beats per minute. He exhibited slow motor function, poor fine motor control, and diffuse muscle tenderness in all 4 extremities. He had decreased (4/5) muscle strength bilaterally with normal and symmetric reflexes. The rest of his examination was normal.

In the emergency room, his serum potassium was 1.9 meq/L, serum glucose 92 mg/dL, serum sodium 135 meq/L, serum chloride 107 meq/L, and serum bicarbonate 19 meq/L, with an anion gap of 9 demonstrating a hyperchloremic nonanion gap metabolic acidosis. Serum albumin was 3.9 mg/dL and serum phosphorus was markedly low at 1.2 mg/dL. Other laboratory values of note at admit are as follows: urine sodium 35 meq/L, urine potassium 7 meq/L, and urine creatinine 15 meq/L (urine anion gap 12), with a fractional excretion of sodium 4.1%. A urine analysis showed a urine pH of 5.5, 30 mg/dL of protein, glucose 500 mg/dL, myoglobinuria, and a negative urine Wrights' stain.

Creatinine kinase was elevated at 755 U/L. His serum creatinine had increased to 2.5 mg/dL (1 month back, his creatinine had been 1.3). Complete blood count and serum magnesium was normal; serum protein electrophoresis did not reveal gammopathy, and a urine protein electrophoresis was not conducted.

Fanconi's syndrome was suspected in this patient given the presence of a hyperchloremic nonanion gap metabolic acidosis, hypokalemia, hypophosphatemia, glucosuria, 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

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3 mEq/L for the first 5 days of hospitalization. Phosphorus was also replaced orally.

The patient's muscle weakness, myalgias, and dyspnea improved dramatically in the first 12 hours of hospitalization, with normalization of his creatinine kinase. The patient's renal function also improved during hospitalization, and upon discharge on hospital day #7 his creatinine had stabilized at 2.2 mg/dL. He was sent home with oral potassium and phosphorus supplementation. Two weeks after discharge, he had follow-up blood tests, which showed that his serum creatinine was 1.5 mg/dL, potassium 3.1 meq/L, and serum bicarbonate 25 meq/L. A repeat urine analysis showed a pH of 6.5 with mild proteinuria and glucosuria. A year after discharge at follow-up, his urine analysis had completely normalized. He is currently doing well, with no long-term sequelae resulting from his renal failure.

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 in 40,000 births. Cystinosis is the most common inherited condition associated with FS, but galactosemia, Wilson's disease, tyrosinemia, and hereditary fructose intolerance may all cause FS. Acquired causes include multiple myeloma, light-chain deposition disease, renal transplantation, and medications, a topic that will be further discussed later. Multiple myeloma is the most common cause of FS in adults and causes renal injury by incomplete obstruction of renal tubules by monoclonal light chains.[8]

There is a high concentration of mitochondrial organelles that populate the proximal tubular cells. This is needed to satisfy the high-energy requirement for driving sodium-potassium pumps. Inherited mitochondrial disease affecting the kidney most commonly takes the form of proximal renal tubular dysfunction (PRTD), otherwise known as FS.

This is characterized by a generalized defect in proximal tubular function with subsequent aminoaciduria, glucosuria with normal serum glucose, and phosphate wasting.[9]

The acidosis that occurs in patients with FS is due to defective bicarbonate reabsorption in the proximal tubule. The amount of filtered bicarbonate decreases until a new threshold is established and all filtered bicarbonate is then again reabsorbed, resulting in a persistent metabolic acidosis.[10] Hypophosphotemia also occurs secondary to poor proximal tubular reabsorption. Severe hypokalemia alone or in conjunction with hypophosphatemia can lead to spontaneous rhabdomyolysis and there are other reported case reports of renal tubular acidosis presenting with rhabdomyolysis and muscle weakness.[11,12]

Polyuria occurs in FS because of osmotic diuresis of glucose and a concentrating defect in the distal tubule and collecting ducts, which may be worsened by hypokalemia.[8]

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.[9]

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 antiretrovirals have been implicated in causing FS, namely cidofovir, adefovir,[9] and 1 case of didanosine.[14]

Tenofovir was initially introduced in the United States in October 2001. It is closely related to the nucleotide reverse transcriptase inhibitor adefovir, which is no longer being used for the treatment of HIV but is in use at a lower dose in hepatitis B virus therapy. Adefovir was associated with PRTD in approximately 50% of HIV-infected patients in a large multicenter trial.[15]

Tenofovir disoproxil fumarate is the first and only nucleotide reverse transcriptase inhibitor approved for the treatment of HIV in combination with other antiretrovirals. Data from numerous clinical studies have highlighted tenofovir's convenience, potency, safety, tolerability, and unique resistance profile. It has a much-touted decreased mitochondrial toxicity and superior efficacy as compared with nucleoside analogs,[16] supporting its use in all stages of HIV infection. The number of patients on tenofovir has increased exponentially. As a standalone molecule and as a component of Truvada®, tenofovir has become the second most widely prescribed antiretroviral agent.[17]

The use of adefovir and cidofovir has been limited because of nephrotoxicity. Tenofovir has been favored for its excellent safety profile, particularly its lack of nephrotoxicity. Two randomized, double-blind studies have described renal tolerance of tenofovir and have found that there was no significant difference between tenofovir (75 to 300 mg/day) and placebo in incidence of renal insufficiency, glucosuria, hypouricemia, and hypokalemia.[18] However, the first case of FS and renal failure due to tenofovir was reported in December 2002.[1] Then, in April 2003, 4 more cases were reported in France in 2 separate publications.[2,3] Karras et al. described 3 cases similar to the case reported here. These patients had had HIV infection for several years and had received other courses of antiretroviral therapies before starting tenofovir. All these patients had normal baseline renal function, but a slight increase in creatinine was noted a few weeks after initiation of tenofovir. However, the drug was not stopped at that time. Then, several months (6 to 11) after initiation of tenofovir therapy, the patients experienced a rapid decline in renal function and classic signs of FS. Discontinuation of antiretroviral therapy led to normalization of proteinuria, acidosis, hypokalemia, and hypophosphatemia in less than 2 weeks. Improvement in renal function was noted in 1 patient but the other 2 had a persistently elevated creatinine, which indicates that there may be some partially irreversible renal damage.[3]

Prolonged renal dysfunction has also been reported by Rifkin, who noted that renal dysfunction can be reported as far out as 18 months with tenofovir-based therapy.[19]

Argument against the association of tenofovir and higher rates of nephrotoxicity is made by an elegant cohort and case control study performed by Jones et al.,[20] showing no significant increase in renal dysfunction in patients taking tenofovir compared with other antiretroviral drugs. In a study of 4,183 HIV-positive patients, 1,175 were identified as having a creati-

nine over 1.2 mg/dL. A comparison of antiretroviral-naive patients and patients exposed to tenofovir and nontenofovir-containing regimens surprisingly revealed a lower rate ratio and probability of developing a creatinine value >1.2 mg/dL in patients exposed to tenofovir (rate ratio vs no antiretrovirals = 0.22, 95% confidence interval [CI]: 0.07 to 0.69; $P<0.001$), with no significant difference between antiretroviral therapy regimens, corrected for duration of therapy. Of the 1,058 individuals on tenofovir, 84 (8%) patients had a creatinine value >1.2 mg/dL subsequent to exposure, with an alternative cause of renal failure in 75 (90%) of these individuals.

However, it is important to note that the focus of this article is to highlight the unique association of FS with tenofovir. No other currently prescribed anti-HIV therapy has been linked to the development of FS consistently.

Our patient had been taking tenofovir for 6 months before presentation. A close review of his serum potassium and creatinine shows evolving hypokalemia and declining renal function during this period (Figure S1). With the discontinuation of tenofovir, his metabolic abnormalities gradually resolved.

CONCLUSION

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 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 antiretroviral therapy.

REFERENCES

1. **Verhelst D, Monge M, Meynard J, et al.** Fanconi's syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2002;40:1331–33.
2. **Creput C, Gonzalez-Canali G, Hill G, Piketty C, Kazatchkine M, Nochy D.** Renal lesions in HIV-1-positive patient treated with tenofovir. AIDS. 2003;17:935–7.
3. **Karras A, Lafaurie M, Furco A, et al.** Tenofovir-related nephrotoxicity in human Immunodeficiency virus-infected patients: three cases of renal failure, Fanconi's syndrome and nephrogenic diabetes insipidus. Clin Infect Dis. 2003;36:1070–73.
4. **Reynes J, Peyriere H, de Merle Boever C, Le Moing V.** Renal tubular injury and severe hypophosphotemia (Fanconi's syndrome) associated with tenofovir therapy. 10th CROI, Seattle. February 9–14, 2002. Abstract 717.
5. **James CW, Steinhaus MC, Szabo S, Dressler RM.** Tenofovir-related nephrotoxicity: case report and review of the literature. Pharmacotherapy. 2004;24:414–8.
6. **Peyrière H, Reynes J, Rouanet I, Daniel N, Merle de Boever C.** Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. J AIDS. 2004;35:269–73.
7. **Earle KE, Seneviratne T, Shaker J, Sboback D.** Fanconi's syndrome in HIV+ adults: report of three cases and literature review. J Bone Miner Res. 2004;19:714.
8. **Lacy M, Gertz M.** Acquired Fanconi's syndrome associated with monoclonal gammopathies. Hem/Oncol Clin N Am. 1999;13:1273–80.
9. **Izzedine H, Launay-Vacher V, Isnard-Bagnis C, Deray G.** Drug-induced Fanconi's syndrome. Am J Kidney Dis. 2003;41:292–309.
10. **Baum M.** The cellular basis of Fanconi syndrome. Hosp Practice. 1993;137–48.
11. **Zanoteli E, De Oliveira AS, Tengan CH, Morita MP, Schmidt B, Gabbai AA.** Distal renal tubular acidosis presenting with rhabdomyolysis. Arquivos de Neuro-Psiquiatra. 1994;52:549–53.
12. **Hanip M, Cheong I, Chin G, Khalid B.** Rhabdomyolysis associated with hypokalemic periodic paralysis of renal tubular acidosis. Singapore Med J. 1990;31:159–61.
13. **Melnick J, Baum M, Thompson J.** Aminoglycoside-induced Fanconi's syndrome. Am J Kidney Dis. 1994;23:118–22.
14. **Crowther MA, Callaghan W, Hodsman AB, et al.** Dideoxyinosine-associated nephrotoxicity. AIDS. 1993;7:131–2.
15. **Kahn J, Lagakos S, Wulfsohn M, et al.** Efficacy and safety of adefovir dipivoxil with antiretroviral therapy: a randomized controlled trial. JAMA. 1999;282:2305–12.
16. **Birkus G, Hitchcock MJ, Cihlar T.** Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother. 2002;46:716–23.
17. **Gilead Marketed Products.** 2005. Annual report. Available at: http://www.gilead.com. Accessed July 2, 2005.
18. **Thompson M.** Clinical update on antiviral drugs. ICAR, 2000. Tenofovir: GS-00-902 and GS-00-907 Studies. Foster City, CA: Gilead Sciences; 2000.
19. **Brian SR, Mark AP.** Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. Am J Med. 2004;117:282–4.
20. **Jones R, Stebbing J, Nelson M, Moyle G.** Renal dysfunction with tenofovir-containing highly active antiretroviral therapy regimens: a cohort and case-control study. J AIDS. 2004;37:1489–95.

Supplementary Material

The following supplementary material is available for this article online at www.blackwell-synergy.com

Figure S1. Serum Creatinine and Serum Potassium Trends in a Patient on Tenofovir Therapy.