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Case Report

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Tenofovir-related acute kidney injury and proximal tubule dysfunction precipitated by diclofenac: a case of drug-drug interaction

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Key words
acute kidney injury – renal Fanconi syndrome – tenofovir – nonsteroidal antiinflammatory drugs – multidrug resistance protein 4

Abstract. We describe an HIV1-positive patient under long-term tenofovir treatment who developed a severe, biopsy-proven, acute tubular necrosis with proximal tubule (PT) dysfunction, precipitated by the very recent start of diclofenac, a nonsteroidal antiinflammatory drug (NSAID). Recent studies show that NSAIDs not only alter glomerular filtration but also multidrug resistance protein (MRP) 4-mediated PT secretion of several substrates. Since the patient tolerated tenofovir well for several years prior to diclofenac use, our observation suggests that diclofenac interfered with tenofovir clearance, thereby favoring its nephrotoxicity. NSAIDs should be avoided in patients under tenofovir.

Introduction

Tenofovir disoproxil fumarate (DF) – the prodrug of the acyclic nucleotide reverse transcriptase inhibitor tenofovir (Viread, Gilead Sciences, Inc., Foster City, CA, USA) – is an efficient and convenient antiretroviral drug with a safe global, mitochondrial and renal profile, as demonstrated by available in vitro [Cihlar et al. 2002] and in vivo data, including large randomized clinical trials [Gallant et al. 2004, 2006, Izzedine et al. 2005]. However, animal studies have suggested that higher doses of tenofovir DF could lead to acute kidney injury (AKI) and proximal tubule (PT) dysfunction [FDA Report 2001], and several cases of AKI and/or renal Fanconi syndrome have been reported since the initial description in 2003 [Verhelst et al. 2003]. Clinical features of tenofovir-related AKI were recently reviewed [Zimmermann et al. 2006]. Kidney biopsies have been rarely performed in patients with tenofovir-induced AKI. The main lesion is an extensive necrosis of epithelial cells lining the PT [Creput et al. 2003, Karras et al. 2003, Schaaf et al. 2003, Verhelst et al. 2003, Zimmermann et al. 2006], sometimes associated with cell vacuolation and/or atrophy, fading of the brush border and dysmorphic, enlarged nuclei. The coexistence of marked interstitial fibro-edema and an inflammatory infiltrate was reported in 5 of the 8 biopsy-proven cases [Creput et al. 2003, Karras et al. 2003, Peyrière et al. 2004, Schaaf et al. 2003, Zimmermann et al. 2006]. Several factors have been associated with increased tenofovir nephrotoxicity, notably the use of concomitant nephrotoxic medications. The most commonly incriminated drugs – besides antibiotics – were pentamidine (4%) and NSAIDs (3%) [Madeddu et al. 2008, Nelson et al. 2007]. We report here an HIV1-positive patient under long-term tenofovir DF who developed a severe AKI with PT dysfunction, triggered by the very recent start of diclofenac.

Case report

A 54-year-old Black African woman was referred to the intensive care unit for polyuria, acute renal failure and severe metabolic acidosis in February 2008.

HIV1 seropositivity had been diagnosed in 1990. Since 2004, her daily highly active antiretroviral therapy (HAART) consisted of lopinavir-ritonavir 133/33 mg, lamivudine 300 mg and tenofovir DF 300 mg. Her past medical history also included Type 2 diabetes mellitus, formerly treated with metformine. Two months before admission, serum creatinine and urea levels were 1.3 mg/dl (115 μmol/l) and 30 mg/dl (5.0 mmol/l), respectively, with an estimated glomerular filtration rate (eGFR) of 62 ml/min/1.73 m^2 (abbrevi-

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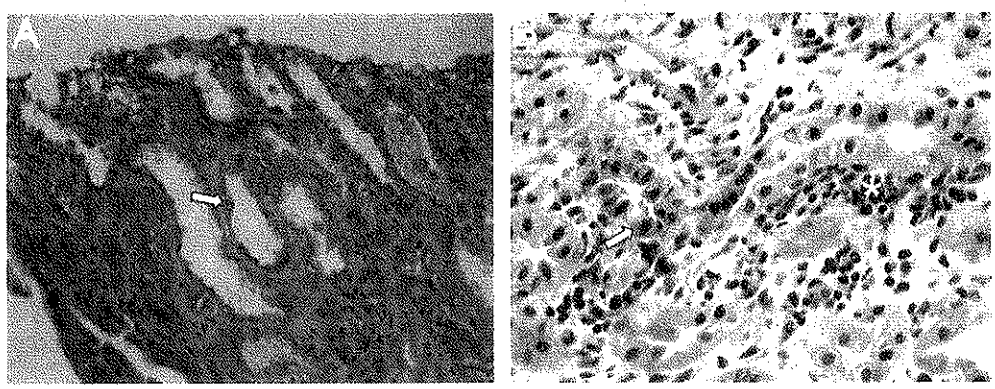

Figure 1. Renal biopsy. A: Light microscopy of the renal cortex showing extensive flattened proximal tubule (PT) epithelial cells (arrow), loss of brush borders and epithelial cells sloughed off the tubular basement membrane (Masson trichrome, × 20). B: Enlarged, dysmorphic, hyperchromatic nuclei (arrow) of PT cells without viral inclusion. Interstitial oedema with focal infiltration by inflammatory cells (asterisk) (hematoxylin and eosin (× 40).

Table 1. Evolution of creatinine, eGFR and PT function.

	Admission	Month 1	Month 2	Month 3	Month 5
Serum creatinine (mg/dl)	9.7	3.8	3.4	2.5	2.2
Serum creatinine (µmol/l)	857	335	300	221	194
eGFR (ml/min/1.73 m^2)	< 5	13	15	21	25
24 h-proteinuria (g/24 h)	2.5	1.95	1.85	1.38	1.62
Glycosuria	(+)	(+)	(–)	(–)	(–)
FE PO_4 (%)	82	N/A	52	33	20
$TmPO_4$/GFR (mg/dl)	0.88	N/A	1.33	2.26	2.47
FE uric acid (%)	N/A	81	N/A	18	17
Aminoaciduria	(+++)	(+)	N/A	(–)	N/A
β_2-microglobulinuria (mg/l)	4.22	95.6	99.5	99.4	92.3

eGFR = estimated glomerular filtration rate by the abbreviated MDRD equation, FE PO_4 = the fractional excretion of phosphate, $TmPO_4$ = the maximal reabsorptive ability for phosphate, N/A = not available. Normal values are as follows: eGFR > 90 ml/min/1.73 m^2, FE PO_4 15 – 20%, $TmPO_4$/GFR > 2.38 mg/dl, and β_2-microglobulinuria < 0.3 mg/l.

ated MDRD equation). Glycated hemoglobin was 5.3% and CD4 level 604/µl, with a viral load of 287 copies/ml.

Five days before admission, diclofenac was started for persistent pain in the lower limbs. Two days later, the patient complained of polyuria and became progressively confused.

On physical examination, she appeared ill, somnolent and disoriented. Temperature was 36.2 °C, blood pressure 122/77 mmHg without orthostatic hypotension, and heart rate 72/min. There was no evidence of dehydration or rash. Laboratory tests disclosed an acute rise in serum creatinine (9.3 mg/dl, 822 µmol/l) and urea (199 mg/dl, 33.1 mmol/l), hyperkalemia (7.1 mEq/l) and severe high anion-gap metabolic acidosis (pH 7.13, bicarbonate 8 mEq/l, plasmatic anion-gap 24). Urinalysis showed proteinuria (2.5 g/day), normoglycemic glycosuria, generalized aminoaciduria, high excretion of β_2-microglobulin and phosphate wasting (Table 1); no crystals were found. Autoimmune serology was negative and complement C3 and C4 levels were within the normal range. No monoclonal protein was detected in blood or urine. Polyuria was confirmed (7 l/day), with urine osmolality at 335 mOsm/kg. Fractional excretion of sodium and urea was 51 and 93%, respectively. Blood and urine cultures remained sterile, and toxicologic screening performed repeatedly on early blood samples did not reveal any toxic agent, including alco-

hols and metformine. Kidney ultrasonography excluded an obstructive uropathy.

A kidney biopsy was performed on Day 5 and showed extensive tubular lesions characterized by flattened epithelial cells often sloughed off the tubular basement membrane, containing dysmorphic enlarged hyperchromatic nuclei without viral inclusions. Multifocal, mild to moderate, infiltration of the interstitium by mixed inflammatory cells and edema with few segmental lesions of tubulitis or interstitial leakage of intratubular proteinaceous material were noted. Quite prominent interstitial hemorrhage, possibly of traumatic origin, was found in the medulla. Interstitial fibrosis and tubular atrophy were not prominent features (Figure 1). There was no glomerular or vascular damage and immunofluorescence with antiimmunoglobulin and anti-C3 antibodies was negative.

The association of severe ATN with partial Fanconi syndrome and impaired urine concentration ability was suggestive of tenofovir-associated AKI. HAART and diclofenac were stopped. No renal replacement therapy was required and renal function started to improve on Day 12. She was discharged from hospital on Day 22, with a serum creatinine of 6.4 mg/dl. At 5 months, eGFR was still 25 ml/min/1.73 m^2. PT function also improved, with complete recovery of glycosuria, aminoaciduria and phosphate wasting after 2, 3 and 5 months, respectively. Still, significant tubular proteinuria persisted (Table 1).

Discussion

We describe an HIV1-positive patient who developed a severe biopsy-proven ATN associated with PT dysfunction and impaired urine concentration ability, suggestive of tenofovir-related AKI. Interestingly, the severe nephrotoxicity of tenofovir DF, which was part of the well-tolerated antiretroviral regimen for more than 4 years, was triggered by the recent start of diclofenac.

Previous observations have suggested a link between tenofovir DF toxicity and the use of NSAIDs. In 2 patients treated with that antiretroviral drug for 25 and 11 months, AKI and renal Fanconi syndrome occurred 1 week after the introduction of rofecoxib and diclofenac, respectively [Parsonage et al. 2005]. The retrospective analysis of Canadian reports of tenofovir DF adverse reactions between March 2003 and December 2005 identified ten cases of nephrotoxicity. Among them, three occurred after NSAID initiation [McMorran et al. 2006]. Four additional cases of tenofovir-induced AKI in combination with NSAIDs have recently been reported [Marcotte et al. 2008]. However, 3 of them also exhibited multiple risk factors for NSAIDs-related renal failure, i.e. cirrhosis and severe dehydration, and no kidney biopsy was available.

Recent studies suggest that NSAIDs not only alter glomerular filtration but also PT secretion of distinct substrates, and thus probably impair tenofovir PT secretion. Tenofovir diphosphate – resulting from the hydrolysis and phosphorylation of tenofovir DF – is essentially cleared from the blood by glomerular filtration and active PT secretion [Antoniou et al. 2003, Barditch-Crovo et al. 2001]. In vitro and in vivo investigations of PT secretion of tenofovir have demonstrated a pivotal role of the tubular transporter MRP4, a member of the C subfamily of ATP-binding cassette transporters family. The ATP-dependent uptake of tenofovir was indeed observed in membrane vesicles expressing MRP4, but not in those expressing MRP2. In addition, kidney accumulation of tenofovir was significantly increased in MRP4-deficient mice, with a PT secretion calculated as 46% of control mice [Imaoka et al. 2007].

MRP4, also called ABCC4, transports distinct endogenous molecules involved in cell signalling, including cyclic nucleotides and ADP, as well as eicosanoids, urate, steroid hormones, bile acids and glutathione. In addition, MRP4 is essential in tissue distribution, brain penetration and toxicity of nucleotide analogues [Russel et al. 2008]. Because of its role in drug distribution and excretion, as well as its potential for deleterious drug-drug interactions, basic research for identifying MRP4 inhibitors is important. Two recent studies have evaluated the interactions of various NSAIDs, including diclofenac, with MRP4 activity in membrane vesicles, and shown that NSAIDs inhibit MRP4-mediated transport at physiologically relevant concentrations [El-Sheikh et al. 2007, Reid et al. 2003]. We thus hypothesize that the inhibition of MRP4-mediated PT secretion of

tenofovir by diclofenac led in our case to increased tenofovir toxicity, resulting in AKI and PT dysfunction.

Conclusions

Tenofovir DF is an efficient and convenient nucleotide reverse transcriptase inhibitor with a safe global, mitochondrial and renal profile. Although cases of AKI and PT dysfunction have been associated with tenofovir DF use, most patients display other risk factors, including NSAIDs, predisposing to tenofovir nephrotoxicity and renal failure. Recent observations show that NSAIDs inhibit MRP4 activity, the apical PT transporter of tenofovir. Therefore, NSAIDs should be avoided in HIV-positive patients treated with tenofovir DF. This information should be disseminated not only to physicians but also to HIV positive patients, as NSAIDs are widely available.

References

Antoniou T, Park-Wyllie LY, Tseng AL. Tenofovir: a nucleotide analog for the management of human immunodeficiency virus infection. Pharmacotherapy. 2003; *23:* 29-43.

Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, Kearney BP, Coleman RL, Lamy PD, Kahn JO, McGowan I, Lietman PS. Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother. 2001; *45:* 2733-2739.

Cihlar T, Birkus G, Greenwalt DE, Hitchcock MJ. Tenofovir exhibits low cytotoxicity in various human cell types: comparison with other nucleoside reverse transcriptase inhibitors. Antiviral Res. 2002; *54:* 37-45.

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:* 935-937.

El-Sheikh AA, van den Heuvel JM, Koenderink JB, Russel FG. Interaction of nonsteroidal anti-inflammatory drugs with multidrug resistance protein (MRP) 2/ABCC2- and MRP4/ABCC4-mediated methotrexate transport. J Pharmacol Exp Ther. 2007; *320:* 229-235.

FDA report. Background package for NDA 21-356: VIREAD (tenofovir disoproxil fumarate). http://www.fda.gov/ohrms/dockets/ac/01/slides/3792s1_02_FDA-tenofovir; 2001.

Gallant JE, Strazewski S, Pozniak AL et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral naive patients: a 3-year randomized trial. JAMA. 2004; *292:* 191-201.

Gallant JE, De Jesus E, Arribas JR et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006; *354:* 251-260.

Imaoka T, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir. Mol Pharmacol. 2007; *71:* 619-627.

Izzedine H, Hulot JS, Vittecoq D, Gallant JE, Staszewski S, Launay-Vacher V, Cheng A, Deray G, Study 903 Team. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients. Data from a double-blind randomized active-controlled multicenter study. Nephrol Dial Transplant. 2005; *20:* 743-746.

Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, Legendre C, Martinez F, Molina JM. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003; *36:* 1070-1073.

McMorran M. Tenofovir (Viread) and NSAIDs: acute renal failure. Canadian Adverse Reaction Newsletter. 2006; *16:* 1-2.

Madeddu G, Bonfanti P, De Socio GV Carradori S, Grosso C, Marconi P, Penco G, Rosella E, Miccolis S, Melzi S, Mura MS, Landonio S, Ricci E, Quirino T, for the CISAI Group. Tenofovir renal safety in HIV-infected patients: results from the SCOLTA project. Biomed Pharmacother. 2008; *62:* 6-11.

Marcotte S, Talbot A, Trottier B. Acute renal failure in four HIV-infected patients: potential association with tenofovir and nonsteroidal antiinflammatory drugs. Can J Infect Dis Med Microbiol. 2008; *19:* 75-76.

Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, Lazzarin A, Schewe K, Lange J, Wyatt C, Curtis S, Chen SS, Smith S, Bischofberger N, Rooney JF. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007; *21:* 1273-1281.

Parsonage MJ, Wilkins EG, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. HIV Med. 2005; *6:* 341-346.

Peyrière H, Reynes J, Rouanet I, Daniel N, de Boever CM, Mauboussin JM, Leray H, Moachon L, Vincent D, Salmon-Céron D. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. J Acquir Immune Defic Syndr. 2004; *35:* 269-273.

Reid G, Wielinga P, Zelcer N, van der Heijden I, Kuil A, de Haas M, Wijnholds J, Borst P. The human multidrug resistance protein MRP4 functions as a prostaglandin efflux transporter and is inhibited by nonsteroidal anti-inflammatory drugs. Proc Natl Acad Sci USA. 2003; *100:* 9244-9249.

Russel FG, Koenderink JB, Masereeuw R. Multidrug resistance protein 4 (MRP4/ABBC4): a versatile efflux transporter for drugs and signalling molecules. Trends Pharmacol Sci. 2008; *29:* 200-207.

Schaaf B, Aries SP, Kramme E, Steinhoff J, Dalhoff K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clin Infect Dis. 2003; *37:* e41-43.

Verhelst D, Monge M, Meynard JL, Fouqueray B, Mougenot B, Girard PM, Ronco P, Rossert J. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2003; *40:* 1331-1333.

Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. Clin Infect Dis. 2006; *42:* 283-290.