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Tenofovir-induced Fanconi syndrome and renal failure

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ABSTRACT

The recent advent of more potent antiretroviral drugs and their combination as part of Highly Active Antiretroviral Therapy (HAART) in patients infected by Human Immunodeficiency Virus (HIV) are known causes of nephrotoxicity. Tenofovir belongs to the nucleotide analogue reverse transcriptase inhibitor (NRTI) class of antiretroviral drugs approved for HIV treatment. Although its nephrotoxicity is considered to be less than that induced by other NRTIs, including cidofovir and adefovir, there have been cases of tenofovir-related renal failure, Fanconi syndrome and diabetes insipidus. The incidence of tenofovir-induced nephrotoxicity is not known, but is estimated to reach 5 to 7% during the first six months of treatment. It only leads to tenofovir withdrawal in 1 to 4%. We report the case of an HIV-infected patient who developed progressive renal failure and Fanconi syndrome while receiving tenofovir. In addition, we discuss the renal manifestations induced by tenofovir and their pathogeny, diagnosis, treatment and prognosis.

Key-Words:
Fanconi syndrome; HIV; renal failure; tenofovir.

CASE REPORT

A 37 year-old HIV-infected male was referred to our hospital in September 2004 to study a new-onset renal failure. A former intravenous drug user, he was enrolled in a methadone treatment programme and reported occasional cannabis and cocaine consumption. Previously diagnosed with chronic hepatitis C virus, he did not tolerate ribavirin and interferon because of depression. In 1994 he was diagnosed with AIDS, with CD4 T-lymphocyte count 360/μL and viraemia undetectable at the time of active pulmonary tuberculosis and ophthalmic herpes zoster infection, thus falling into the C2 subcategory criteria of HIV infection. HAART was started along with specific tuberculosis and ophthalmic herpes zoster therapy. In February 2003 his antiretroviral regimen was modified to tenofovir plus lopinavir/ritonavir, with the rest of his treatment consisting of methadone, calcium carbonate and potassium aspartate. On admission the patient had blood pressure 132/93 mm Hg and weighed 48kg. He was mildly dehydrated and had a cachectic *habitus*. Other physical examination results were unremarkable, except for a non-tender hepatomegaly. Initial laboratory tests revealed serum creatinine

Table I

Laboratory tests evolution

	Cr (mg/dl)	Urea (mg/dl)	FA (UI/l)	Urate (mg/dl)	Lactate (mg/dl)	Phosphorus (mg/dl)	Potassium (mEq/L)	Urinary Protein (gr/24h)
05/02/2004	1.5	51	395	2.7	28.5	–	–	0.6
19/05/2004	1.5	46	781	2.9	21.9	–	–	0.6
07/09/2004	4.2	111	1234	3	10.1	1.8	3.5	3.8
27/09/2004	3.3	68	1216	2.9	17.4	3.2	3.3	2.6
06/10/2004	2.2	52	438	–	–	3	3.5	0.6

3.2 mg/dL (283 µmol/L), urea 69 mg/dL (24.6 mmol/L), calcium 7.8 mg/dL (1.94 mmol/L), phosphorus 2.2 mg/dL (0.71 mmol/L), cholecalciferol 9 ng/mL, total protein 6.9 g/dL, potassium 4.1 mmol/L, sodium 138 mmol/L, plasmatic osmolality 299 mOsm/L and bicarbonate 15 mmol/L with a normal anion gap. The evolution of the laboratory tests are shown in Table I.

Urinalysis showed moderate proteinuria (1.4 g/day), few leucocytes, alkaline pH 8, moderate glycosuria ++, hyperuricosuria 21.1 ml/min and hypercalciuria 288 mg/day. No monoclonal component was found. Cryoglobulins were negative as were immune markers. Posterior laboratory studies confirmed the diagnosis of Fanconi syndrome consisting of a $TmHCO_3^-$ ‹15, normoglycaemic glycosuria and generalised aminoaciduria. However, during hospitalisation proteinuric losses reached 3.5 g/day, thus implying some form of glomerular involvement. A renal biopsy (Fig. 1) was performed, providing evidence of a mild mesangioproliferative glomerulonephritis with associated images suggestive of stage II membranous nephropathy. Acute focal tubulo-interstitial nephritis with focal tubular atrophy and necrosis were also present. Vessels showed moderate arteriolosclerosis and hyalinosis.

We also performed a radionuclide bone-scintigraphy that showed a diffusely increased accumulation of the marker with focal deposit at the left lower ribs, compatible with osteomalacia. Tenofovir was stopped on 9th September 2004 and Fanconi syndrome disappeared subsequently with a parallel complete remission of renal failure. We initiated supplements of potassium, sodium, bicarbonate, calcium and cholecalciferol. Posterior laboratory assessment revealed a moderate proteinuria of 1g/day.

DISCUSSION

NRTI-associated nephrotoxicity, such as that encountered with adefovir and cidofovir, is closely related to the molecule's excretion pathway. HOAT1 is an organic-anion transporter, expressed by the epithelium of the proximal tubule in the human kidney, which allows transfer of NRTIs from bloodstream to cell, the first step towards nephrotoxicity. This has been demonstrated *in vitro* for adefovir and cidofovir.

Other experiments suggest a possible mitochondrial toxic effect of tenofovir, although this seems of little relevance[1]. Yet, high-dose tenofovir triggers acute renal failure and proximal-tubule damage, as evidenced in animal studies. Moreover this effect was shown to be dose-dependent[2].

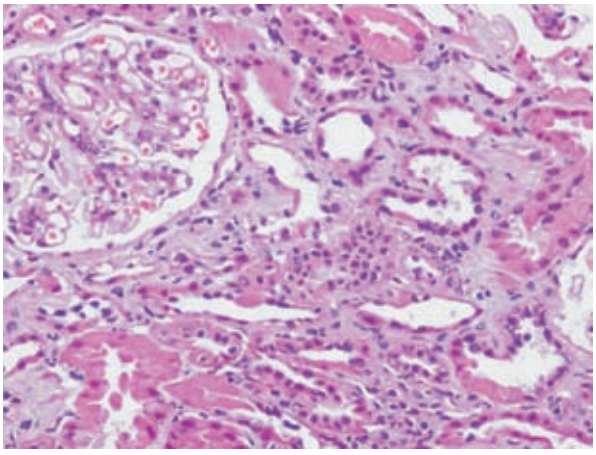

Fig. 1 – Renal Biopsy: Mild mesangioproliferative glomerulonephritis with associated images suggestive of stage II membranous nephropathy. Acute focal tubulo-interstitial nephritis with focal tubular atrophy and necrosis were also present. Vessels showed moderate arteriolosclerosis and hyalinosis

It has been suggested that tenofovir-related renal toxicity is most prevalent among patients with low weight, previously altered renal function or previous and prolonged treatment with reverse transcriptase inhibitors ritonavir and other nephrotoxic agents[1-5]. In our case, it is likely that the conjunction of low weight, previous renal injury and ritonavir favoured the development of kidney injury. Time of onset of clinically overt nephropathy after beginning tenofovir is variable, generally taking between 4 to 7 weeks of drug exposure, while sometimes it might take up to several months before renal toxicity emerges[1,2]. Until now tenofovir's renal toxicity has been associated with Fanconi syndrome, diabetes insipidus and renal failure due to interstitial nephritis, but there is currently no reference in the literature of an associated glomerular involvement. In general, the proximal tubule is involved, the interstitium shows mixed type focal inflammatory infiltrates but the vessels and glomeruli are spared.

In our case, glomerular involvement could be explained by HCV infection alone, although we cannot rule out tenofovir as the primary cause. Indeed, the development of nephrotoxicity has a temporal relationship with tenofovir administration. Moreover, partial recovery from renal failure and proteinuria with total resolution of Fanconi syndrome after discontinuation of the drug are strong arguments supporting this hypothesis, despite the fact that no corticosteroid therapy was given. Discontinuation of tenofovir, is, however, always followed by rapid improvement of renal failure, remission of diabetes insipidus and resolution of Fanconi syndrome. Some animal studies show osteomalacia as being potentially reversible, but other reports do not mention this topic. In our case, alkaline phosphatase fell progressively to normal levels.

We conclude that renal changes produced by tenofovir could be prevented through detection of high risk groups and a close monitoring of serum creatinine values and other biological markers including serum uric acid, urinary protein, glucose and osmolality. Testing for tenofovir therapeutic blood levels could prove to be useful but more studies are needed to determine its usefulness in humans. A renal biopsy is indicated whenever interruption of the suspect drug is not accompanied by a parallel recovery or if there is a high index of suspicion of another concomitant nephropathy.

Conflict of interest statement. None declared.

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