

Tenofovir-associated Fanconi syndrome and hypophosphatemic rickets in a girl infected with HIV

Síndrome de Fanconi y raquitismo hipofosfatémico asociado al uso de tenofovir en una niña infectada con VIH

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Abstract

Introduction: Tenofovir (TDF) is an inhibitor of reverse transcriptase nucleotide analogue, although it has good tolerability and high anti-retroviral activity, its effect on the kidney has been a concern.

Objective: To describe a girl infected with HIV who presented Fanconi syndrome during antiretroviral therapy with TDF. **Clinical case:** We describe a HIV-1-infected girl, who after 18 months treatment with TDF presented loss of strength and pain of the lower extremities with functional impairment. Laboratory findings were consistent with Fanconi syndrome. Radiographs showed bilateral fracture of the hip and wrists. Full recovery of Fanconi syndrome was achieved four months after changing antiretroviral therapy. **Conclusions:** TDF-prescribing physicians must be prepared to detect signs and symptoms of renal dysfunction and immediately consider switching to another antiviral drug.

Keywords:

Renal tubulopathies;
Drug-related
side effects;
Hypophosphatemic
rickets;
HIV.

Introduction

Morbidity and mortality associated with human immunodeficiency virus (HIV) infection has declined considerably after the introduction of highly effective antiretroviral therapy. However, various adverse effects have been described with the use of this therapy over a long time¹.

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue that blocks the action of reverse transcriptase². Despite its good tolerance and high antiretroviral effectiveness, it can cause cumulative renal damage. TDF is eliminated by glomerular filtration and proximal tubular secretion. About 20-30% of the drug is actively transported in the renal proximal tubule cells through organic anion transporters located in the ba-

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solateral membrane. Subsequently, the drug is secreted into the tubular lumen by the transporters of the apical membrane^{3,4}.

A recent systematic review of the literature showed a modest decrease in creatinine clearance in patients who used TDF⁵. However, some reports have described the development of symptomatic renal dysfunction: proximal tubulopathies, osteomalacia, diabetes insipidus and acute renal failure in relation to the use of this drug^{6,7}. The renal safety of TDF in children and adolescents has not been well documented, although there are sporadic reports of renal toxicity. However, Virgano et al. described renal safety in the treatment of TDF after 96 weeks of use in children^{8,9}.

The aim of this report is to present the case of an HIV-infected girl with symptoms and laboratory findings compatible with Fanconi syndrome during treatment with TDF as part of her antiretroviral therapy.

Clinical case

An 11-year-old patient with a history of congenital HIV, diagnosed at 6 years of age at stage N3 (clinical category "N" corresponds to the asymptomatic infected child and stage "3" corresponds to severe immunosuppression). Highly active antiretroviral therapy was started 6 months later. She presented low levels of adherence to the treatment, and after 4 years a high viral load was confirmed. Viral genotyping was performed which showed resistance to the three antivirals used. It was decided to change therapy to Kaletra® (lopinavir

80/ritonavir 20) (3.5 ml every 12 h), abacavir (300 mg every 12 h) and TDF (300 mg daily), which presented good adherence and a decrease of viral loads. After 18 months of therapy, she presented loss of strength, lower extremity pain, functional disability, difficulty in swallowing and weight loss. Upon admission, she had a BMI of 14.5, which is in the 10th percentile (z -1.9) of her age, and a height/age z -1.7 SD.

Laboratory studies showed hypophosphatemia, elevated alkaline phosphatases, metabolic acidosis, an elevated calcium/creatinine ratio, decreased phosphate tubular reabsorption, glucosuria and proteinuria (Table 1). Nuclear magnetic resonance and renal ultrasound were normal. Bone densitometry showed a significant decrease in bone mineral density.

Based on this, proximal renal tubular acidosis (Fanconi syndrome) and secondary hypophosphatemic rickets were suspected. Treatment was started with phosphorus (40 mg/kg/day), vitamin D (1,000 U per day), sodium bicarbonate 1 g every 6 h. Antiretroviral therapy was kept and the patient started control. The patient returned 4 months later presenting painful walking and widening of the wrists, and maintaining her nutritional state. X-rays showed bilateral fractures of the hip and wrists (Figure 1).

The case was presented to the pediatric AIDS committee, who considered that TDF caused secondary tubulopathy and switched therapy to Kaletra (lopinavir/ritonavir) (280 mg every 12 h) and raltegravir (200 mg every 12 h), providing therapy for tubulopathy. Simultaneously, hip osteosynthesis and orthopedic treatment of the fractures of the wrists were performed. Two months after the change in therapy, the

Table 1.

	Basal	2 meses	4 meses
Calcio (mg/dl)	9,6	10,2	9,8
Fósforo (mg/dl)	2,6	5,3	5,3
Fosfatasas alcalinas U/l	660	275	292
Creatinina(mg/dl)	0,9	0,87	0,68
NaCl/KCl/Cl (mEq/l)	139/3,6/103		139/4,2/103
Ph-HCO ₃ mg/dl-BE	7,31-19- -6,2	7,3-21,5- -1,9	7,35-22- -1,9
Razón calcio/creatinina urinaria	0,8	0,08	0,2
TRP %	55%	94%	94%
Calcio-fósforo urinario	94/83	12/104	32/46
Creatinina urinaria (mg/dl)	104	183	102
PTH (pg/ml)	25,9	25,9	
Vitamina 25 OH (ng/ml)	15,4		88,5
Glucosuria- proteinuria	+	-	-

PTH: paratohormona; TRP: reabsorción tubular proximal.

patient gained weight (4 kg), reaching a BMI between p25 to p50 (z-0.5 and 0); tests showed improvement in hypophosphatemia, normal urine, tubular phosphate reabsorption and normal calcium/creatinine ratio. She resumed walking 2 months after surgery.

She recovered fully from Fanconi syndrome 4 months after the change in antiretroviral therapy and her nutritional status remained within the normal curve.

Discussion

Our patient presented Fanconi syndrome and hypophosphatemic rickets with multiple fractures secondary to TDF treatment. Fanconi syndrome is a generalized dysfunction of the renal proximal tubule, characterized mainly by hypophosphatemia due to phosphaturia, renal glucosuria (without hyperglycemia), aminoaciduria and tubular proteinuria of low molecular weight. There may also be mild hypochloremic metabolic acidosis (bicarbonate 15 meq/L), hypovolaemia with polyuria, polydipsia, and hypokalemia¹⁰.

The etiology of Fanconi's syndrome includes inherited and acquired diseases. Genetic conditions associated with this syndrome include Dent disease, cystinosis, tyrosinemia type 1, galactosemia, Wilson's disease, Lowe's syndrome, hereditary fructose intolerance and mitochondrial myopathies. The causes are secondary to drugs and heavy metals. The drugs include anticancer drugs (cisplatin, ifosfamide), antiviral drugs (adefovir, cidofovir and tenofovir), antibiotics (gentamicin, tobramycin and amikacin), anticonvulsant (valproic acid), and those secondary to heavy metals lead, mercury and cadmium¹⁰⁻¹².

In patients with HIV, the main cause of Fanconi syndrome is the use of drugs, mainly TDF and other nucleoside analogs¹³.

There have been few published cases of Fanconi syndrome in children treated with TDF, reporting an incidence rate between 0.5-2%^{8,9,14}. The cases described have also used a protease inhibitor (ritonavir) in highly active antiretroviral therapy, such as our patient. Ritonavir may cause increased plasma levels of some drugs such as TDF which may favor its toxicity^{4,15}.

Pathogenic mechanisms involving the effect of TDF on the kidneys are not well understood, some suggest that accumulation of the drug in the proximal tubules is a key mechanism given its affinity for the organic anion transporter (OAT1)¹⁶. Other studies suggest that there might be genetic factors that would favor this damage, such as affinity for different kidney proteins¹⁷. Recent studies have shown that oxidative stress, inflammation, chronic renal failure, diabetes, malnutrition and the simultaneous prescription of



Figure 1.

other drugs (didanosine and protease inhibitors) may facilitate nephrotoxicity^{18,19}.

As for the time of onset of symptoms, some publications have shown that Fanconi syndrome occurs on average within 10 months (1-24 months) after the introduction of TDF, the time observed in our patient was 18 months.

Secondary to phosphaturia of the Fanconi syndrome, the patient developed hypophosphatemia and a hypophosphatemic rickets. Rickets is the deficiency in the mineralization of the osteoid tissue (new non-mineralized tissue)^{20,21}. The accumulation of non-mineralized bone tissue leads to weakening of the bone in the areas that support weight and to the clinical and radiographic alterations, which was observed in our patient. Hypophosphatemic rickets primarily involves phosphorus and may be due to a deficit in absorption at the gastrointestinal level or renal loss, as in our case.

There is no specific treatment for Fanconi syndrome. The primary measure of treatment is the suspension of the drug involved. Our patient recovered 3 months after stopping therapy, which is consistent with the literature¹⁵. In this case, Fanconi syndrome caused by TDF had a good prognosis; however, irreversible renal damage has been described in the months after initiating therapy²².

There are also no specific and sensitive markers of renal damage by TDF, but for tubular dysfunction increased phosphate excretion apparently is the most sensitive marker. In a Swiss study, phosphaturia was present in 40-50% of patients with PFD, versus 25% of patients with other antiretrovirals and 4% of untreated patients²³.

Considering that a small number of antiretrovirals can be used for children, it is difficult to remove TDF from combination therapy, and therefore doctors prescribing this drug should be alert to detect symptoms and signs suggestive of renal dysfunction and prepare themselves to promptly change the therapy to avoid further side effects.

Ethical Responsibilities

Protection of people and animals: The authors state that no experiments have been performed on humans or animals for this research.

Confidentiality of data: The authors state that they have followed the protocols of their work center on the publication of patient data.

Privacy rights and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflict of interest

The authors declare that they have no conflict of interest.

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