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Fanconi Syndrome Induced by Concomitant HIV PrEP and Tacrolimus

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Abstract

Fanconi syndrome (FS) is a severe grade of drug-induced proximal tubule toxicity. There are numerous causes for acquired FS, and drug toxicity is one of the most common. FS is known to be associated with the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF). TDF is often used in combination with emtricitabine (FTC) for preexposure prophylaxis (PrEP) of human immunodeficiency virus (HIV) infection. TDF/FTC-induced FS has been observed as a dose-related phenomenon that is directly correlated to kidney function, high levels of absorption of the drug into the proximal tubule, and interactions with other medications. This case report describes a patient who acquired FS after starting TDF/FTC for PrEP in the setting of chronic kidney disease (CKD) with concomitant tacrolimus therapy, a known nephrotoxic agent.

Keywords

Fanconi, PrEP, tenofovir, toxicity

Introduction

Fanconi syndrome (FS) is one of the most severe grades of drug-induced proximal tubule toxicity.[1] There are numerous causes for acquired FS, but drug toxicity is one of the most common, with prior studies demonstrating the association that anti-viral medications have with this form of proximal tubule toxicity.[2] FS is associated with the anti-viral tenofovir (TDF), which works as a reverse transcriptase inhibitor and is used in combination with emtricitabine (FTC) for preexposure prophylaxis (PrEP) prevention of human immunodeficiency virus (HIV) infection in unaffected individuals who are in an ongoing relationship with a partner living with HIV.[3] TDF/FTC-induced FS has been observed as a dose-related phenomenon that is directly correlated to kidney function, high levels of absorption of the drug into the proximal tubule, as well as interactions with other medications.[1] Similarly, we report a case of a patient who acquired FS after starting TDF/FTC for PrEP in the setting of chronic kidney disease (CKD) with concomitant tacrolimus therapy, a known nephrotoxic agent. This scenario and interaction underscore the need to consider risk factors which may predispose patients to developing proximal tubule toxicity with TDF/FTC.

Case Report

A female in her early 60s presented to the emergency department (ED) with a chief complaint of sporadic and intractable nausea and vomiting that had been worsening over a 2-week period, acute kidney injury (AKI), hypokalemia, and elevated anion gap metabolic acidosis. Her history revealed numerous visits to the ED over the past year with the same complaint, presentation, and worsening serum creatinine. The diagnostic uncertainty and plan for further workup as an outpatient was discussed with the patient during these ED visits.

The patient's pertinent past medical history to this case is significant for heart transplant due to dilated cardiomyopathy, chronic immunosuppression, stage III CKD diagnosed 5 years prior, and exposure to HIV from her partner. In addition, testing revealed she was negative for HIV, as well as hepatitis B virus (HBV). Her home medication of interest for this case included TDF/FTC 200/300 mg daily, which she was initiated 2 years prior and without dose adjustment for a baseline creatinine clearance (CrCl) of approximately 41 mL/min. The patient was also on tacrolimus and mycophenolate for the past 5 years. Other home medications include clonidine, quetiapine, potassium, pravastatin, oxymorphone,

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Table 1. Baseline and ED Values.

Lab measurement	Value at baseline	ED presentation	Reference
Serum blood draw			
Bicarbonate (mEq/L)	15-21	8	22-30
Anion Gap	18	19	4-15
Potassium (mEq/L)	3.0	3.3	3.5-5.1
Magnesium (mg/dL)	n/a	1.2	1.9-2.7
Phosphorus (mg/dL)	n/a	1.1	2.5-5.0
Calcium (mg/dL)	8	8.6	8.4-10.2
Glucose (mg/dL)	92	109	70-99
Uric acid (mg/dL)	2.0	n/a	2.5-6.2
Tacrolimus (ng/mL)	12.3-25	14.1	8-18 5-10 heart transplant > 6 mos.
Parathyroid hormone (PTH), (pg/mL)	n/a	136	14.5-89.6
Creatinine (mg/dL)	1.4	1.9	0.52-1.04
Blood urea nitrogen (BUN) (mg/dL)	19	14	7-17
Creatinine clearance (ml/min)	41	21	>60
Urine			
Protein (mg/dL)	>500	1,794	Negative
Glucose (mg/dL)	>150	>500	Negative

Abbreviation: ED, emergency department.

and lidocaine patch. The relevant laboratory results from a venous blood draw and a urinalysis, at baseline and presentation to the ED, are shown below in Table 1. At baseline, the patient had an elevated tacrolimus level, and was unsure if she followed through with the recommended dose reduction on a prior outpatient visit.

The patient was ultimately admitted and transferred to the medical floor where she received a normal saline infusion that improved her acute kidney injury to a creatinine of 1.5 mg/dL. On day 2, venous labs revealed ongoing acidosis, with the following values shown below in Table 2, and the patient was transferred to the intensive care unit (ICU) and nephrology consulted.

Arrangements were made with the transplant and infectious diseases (ID) team after the nephrologist requested tacrolimus and TDF/FTC be held due to a possible additive nephrotoxic effect. A sodium bicarbonate intravenous (IV) infusion at a rate of 150 milliequivalents (mEq) over 12 hours, until serum bicarbonate greater than 14, was initiated. The ICU electrolyte replacement protocol for calcium (1 gm IV), potassium (20 mEq), phosphorus (15 mmol), and magnesium (2 gm) was ordered every 2 to 6 hours as needed. The patient was transferred out of the ICU on day 3 and tacrolimus was restarted at a lower dose. Labs on the basic metabolic panel (BMP) were within normal limits by day 6 and the patient stated she was feeling back to baseline. Ultimately, the patient was determined to have TDF/FTC-induced FS based upon her clinical features of proteinuria, hypophosphatemia, normoglycemic glycosuria, metabolic acidosis, hypouricemia, and hypokalemia.[1]

Upon discharge from the hospital, TDF/FTC was not restarted for the patient, and tacrolimus was continued at the reduced dose. The patient also received prescriptions for oral magnesium oxide, potassium chloride, sodium bicarbonate, and potassium phosphate. At follow-up, ID recommended future treatment of PrEP with FTC/tenofovir alafenamide (TAF).

Discussion and Conclusions

Having a limited number of existing reports, FS is a relatively uncommon adverse event for anti-viral agents. This case report is of significance as FS occurred during PrEP therapy, confirmed via diagnosis by improvement in tubule function after withdrawal of the drug.[1] To support the findings from this case, another case report by Iwata et al described FS in a male who acquired HIV secondary to TDF/FTC therapy for standard antiretroviral therapy (ART).[4] This is again supported in a case report by Mugwanya et al, which thoroughly described the effect of TDF-based PrEP along with concomitant nephrotoxic medications to decrease proximal tubule function and induce FS.[5]

In addition, we report the additive nephrotoxic effects, supratherapeutic levels, of tacrolimus in combination with TDF/FTC based PrEP contributed to the development of FS in this case. This interaction has not been reported before in the literature, and this case report is suspected to be the first identifying the risk of concomitant therapy of the 2 agents. Drug–drug interaction (DDI) databases as of now do not mention this interaction.[6] This has the potential for this DDI to be missed, as many electronic health record systems will not flag this interaction, leading to both potentially a failure in identifying this issue, as well as a delay in identifying it. While mycophenolate is also well-known to be nephrotoxic,

Table 2. Day 2-6 Lab Values.

Lab measurement	Day 2	Day 3	Day 4	Day 5	Day 6	Reference
Serum blood draw						
Bicarbonate (mEq/L)	8	12	15	21	19	22-30
Anion gap	16	14	10	13	12	4-15
Potassium (mEq/L)	3.1	3.7	3.6	2.8	4.3	3.5-5.1
Magnesium (mg/dL)	2.9	1.6	1.5	1.6	1.7	1.9-2.7
Phosphorus (mg/dL)	1.1	4.5	2.8	3.3	3.3	2.5-5.0
Calcium (mg/dL)	8.0	7.6	7.0	7.7	7.8	8.4-10.2
Glucose (mg/dL)	95	92	90	85	93	70-99
Uric acid (mg/dL)	n/a	n/a	n/a	n/a	n/a	2.5-6.2
Tacrolimus (ng/mL)	n/a	n/a	6.8	n/a	n/a	8-18 5-10 heart transplant >6 months
Parathyroid hormone (PTH), (pg/mL)	n/a	n/a	n/a	n/a	n/a	14.5-89.6
Creatinine (mg/dL)	1.5	1.3	1.2	1.10	1.10	0.52-1.04
Blood urea nitrogen (BUN) (mg/dL)	14	6	9	9	9	7-17
Creatinine clearance (ml/min)	43	50	55	>60	>60	>60
Urine						
Protein (mg/dL)	n/a	n/a	n/a	n/a	n/a	Negative
Glucose (mg/dL)	500	n/a	n/a	n/a	n/a	Negative

it was not believed to be toxic in this patient and the known medication side effects are not consistent with many of the clinical features of FS.

Overall, in the setting of FS, it is recommended that the offending medication be discontinued immediately and complications be addressed.[1] In this case report, ID and nephrology specialists were promptly consulted on day 2 of admission, facilitating a fairly rapid recognition of this drug-induced adverse event. TDF/FTC for PrEP was initiated in the face of risk factors for FS, including CKD, and proximal tubule complications could have been prevented with the following steps for early detection of renal decline and avoiding compounding or high-risk factors for renal toxicity:

- Establish baseline kidney function prior to initiating TDF, and monitor every 4 weeks in the first year.[1]
- Use caution with other nephrotoxic agents.[3]
- Dose reduce or avoid use when CrCl < 60 mL/min[3].
- Monitor phosphate and vitamin D levels.[4]
- Monitor for potential early symptoms of FS, including polyuria, bone pain, proximal muscle weakness, and fractures.[1]

The patient in this case report developed FS after being initiated on TDF-based PrEP once daily with CKD and a CrCl of 41 mL/min. Due to the baseline kidney function, dosing every other day is recommended instead of the patient's current regimen of a once daily dose. This was not addressed upon initiation and is likely a reason that this patient developed FS, further supporting the above recommended steps for identifying high risk factors of renal toxicity with TDF-based PrEP. When TDF-induced renal disease is recognized in a patient, TDF should generally be discontinued, and alternative therapies explored. In this patient case, the TDF was being used as HIV PrEP, where there are currently only 2 Food and Drug Administration (FDA)-approved medication options. The best alternative at this time would be transition patients to the combination of FTC/ TAF. TAF is a newer generation nucleoside analog that is a prodrug of tenofovir that results in up to 90% less systemic drug exposure than TDF.[7] There is emerging data to support its safety as an alternative in patients that develop renal complications on TDF.[8] However, there have been reports of TAF-induced FS have also been cited.[9] Due to the severity of FS, preventative monitoring and dosing strategies should be implemented as they are essential to mitigate risk of drug-induced kidney damage, which may have profound consequences for patients.

Authors' Note

This case report has been previously presented as a poster in abstract form under the title, "Acute on chronic Fanconi syndrome induced by tenofovir compounded by tacrolimus toxicity," at the American College of Clinical Pharmacy annual meeting in New York, New York, October 2019.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

This case report is exempt through our institution's Institutional Review Board. Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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