# A Case Report of Deferasirox-induced Kidney Injury and Fanconi Syndrome

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## ABSTRACT

Cases of kidney injury associated with the use of deferasirox chelation therapy during the course of treatment for iron overload have been reported infrequently. We present the case of a patient treated with deferasirox who had biopsy-proven tubular injury in the setting of clinical Fanconi syndrome. The patient required hospitalization for metabolic acidosis, electrolyte abnormalities, and associated symptoms. With supportive care and cessation of chelation therapy he improved, but has yet to fully recover. This is the first known case reporting biopsy-proven tubular damage in the setting of deferasirox use.


## INTRODUCTION

High iron stores in the body can result from primary or secondary processes. Several genetic mutations have been identified as causing primary or hereditary hemochromotosis. Patients with these mutations are typically of Northern European descent and develop complications from iron deposition in various organs. The classic triad of bronze skin, diabetes, and liver failure highlights some of the complications of the disease, which can also include arthritis, hypogonadism, cardiomyopathy, and hepatocellular carcinoma. The cornerstone of treatment in these patients is routine phlebotomy.[1]

Secondary iron overload usually results from multiple blood transfusions or a severe hemolytic anemia.[1] Patients with hemoglobinopathies such as thalassemia or sickle cell disease and patients with bone marrow pathology such as myelodysplasia or myelofibrosis often become dependent on routine blood transfusions.[2] Others who develop this acquired form of iron overload may have required a significant number of blood transfusions for a defined period of time—such as during or after treatment of a malignancy. Iron overload syndromes can result in the same complications described above as a result of iron deposition in various tissues.[3] Patients with secondary iron overload cannot tolerate phlebotomy as a treatment option because their primary disease is anemia. Instead, these patients are treated with chelating agents that specifically target iron removal or prevent iron overload from occurring without affecting hemoglobin levels.[3,4]

Chelation therapy has long been considered an inconvenience to both patient and clinician.[4,5] Until 2005, for patients in the United States with iron overload syndromes, chelation therapy meant daily subcutaneous injections and thus frequent medication noncompliance and therapy failure.[4,5] In 2005, the US Food and Drug Administration approved deferasirox (Exjade), an oral chelating agent, intended for use in patients age 2 years and older suffering from iron overload syndromes.[6]

Deferasirox binds iron with high affinity, facilitating iron excretion primarily through the feces. Approximately 8% of the drug and its metabolites are excreted by the kidney. A starting dose of 20 mg/kg/day is recommended with a recommended maximum daily dose of 40 mg/kg. The prescribing package insert recommends reduction of the daily dose of deferasirox by 10 mg/kg if a rise in serum creatinine to >33% above the average pretreatment measurements is seen at 2 consecutive visits, and cannot be attributed to other causes.[6]

Warnings and precautions in the package insert identify the possibility of sometimes-fatal acute renal failure in patients taking deferasirox. Without describing the specific case fatalities, they report that patients at greatest risk are those with advanced age, advanced hematologic disease, or previous renal disease. During clinical trials, 113 out of 296 patients (38%) developed >33% increase in creatinine on 2 consecutive visits. Fanconi syndrome is listed as a rare complication occurring in 0.1% to 1% of patients treated with deferasirox. We found case reports documenting 6 patients who developed Fanconi syndrome in the setting of deferasirox therapy.[6]

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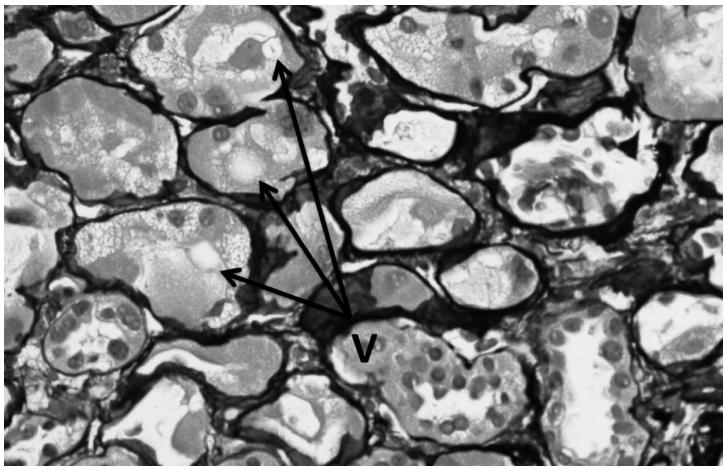
**Table 1.** Patient's Laboratory Results Prior to, During and After Deferasirox Therapy

| | March 2011 | August 2011 | December 2011 | March 2012 | May 2012 |
|---|---|---|---|---|---|
| Serum Potassium | 5.7 | 4 | 3.3 | 2.7 | 3.5 |
| Serum Phosphorus | 2.6 | 2.2 | 2.6 | 1.6 | 2 |
| Serum Creatinine | 1.0 | 1.26 | 1.5 | 2.5 | 1.52 |
| Urine Glucose | trace | 2+ | 3+ | 3+ | 2+ |
| Urine Potassium | | | | 39 | |
| Urine Phosphorus | | | | | 36 |

**Figure 1.** Kidney Biopsy




Silver-stained section from patient's biopsy at 400X magnification. The tubular epithelial cells have marked cytoplasmic vacuolization consistent with drug toxicity—similar to that reported in the animal studies on marmosets and rats administered oral deferasirox.

## CASE DESCRIPTION

Our patient is a 21-year-old male survivor of Ewing sarcoma who developed progressive decline in renal function and Fanconi syndrome after being prescribed deferasirox for treatment of iron overload.

Three years into remission of his Ewing sarcoma, the patient had a ferritin level of 1502 ng/mL (range 20-300 ng/mL) and magnetic resonance imaging (MRI) revealed T2 hypointensities consistent with iron deposition in the liver and spleen. Hemochromotosis gene mutation tests were negative, so iron overload was thought to be secondary to the over 35 blood transfusions he received during the course of treatment for Ewing sarcoma.

The patient was started on deferasirox 1125 mg daily in June 2011, at which time his serum creatinine was 1.1 mg/dL (range 0.7-1.2 mg/dL). His renal function declined progressively while on chelation therapy, with serum creatinine increases to 1.25 mg/dL in August 2011; 1.5 mg/dL in December 2011; 1.84 mg/dL in January 2012; and 2.03 in February 2012. Throughout the months he received chelation therapy, the patient's urinalyses were significant for 1-3+ proteinuria and 2-3+ glycosuria. In early March of 2012, he was admitted to the hospital with abdominal pain, nausea, vomiting, body aches, and anorexia. He was found to have a creatinine of 2.5 mg/dL, bicarbonate of 16 mmol/L (range 22-32 mmol/L), potassium of 2.7 mmol/L (range 3.5-4.8 mmol/L), phosphorous of 2.4 mg/dL (range 2.5-4.5 mg/dL), 1+ proteinuria, and 2+ glycosuria. His random urine potassium was 39 mmol/dL and his transtubular potassium gradient (TTKG) was 11, confirming inappropriate urinary excretion of potassium (Table 1). The patient's urine sediment was bland and urine eosinophils negative. His kidney biopsy revealed severe tubular injury with tubular epithelial cells demonstrating isometric vacuolization consistent with drug toxicity. There was no glomerular injury, arteriolar or interstitial inflammation (Figure 1). Deferasirox was stopped. He was treated with bicarbonate drip and potassium and phosphate repletion. Eleven days after admission, the patient's creatinine improved to 1.5 mg/dL and bicarbonate returned to 24 mmol/L. However, 4 months after deferasirox was stopped, the patient continues to have hypokalemia, hypophosphatemia, proteinuria, and glycosuria and requires daily potassium and phosphate supplementation (Table 1).

## DISCUSSION

Our patient presented with renal insufficiency, proteinuria, glycosuria, hypophosphatemia, hypokalemia, and metabolic acidosis. This constellation of symptoms strongly suggested renal pathology and specifically Fanconi syndrome. A healthy kidney will conserve potassium in the setting of hypokalemia. In a healthy patient with hypokalemia, the random urine potassium level should be no greater than 20-30 mmol/L. Our patient's random potassium level was 39 mmol/L. The TTKG is a calculation that helps to differentiate renal potassium losses from gastrointestinal potassium losses. In the setting of hypokalemia, the TTKG should be less than 3. Our patient's TTKG while hypokalemic was 11. Both the urine potassium and the TTKG measurements confirmed inappropriate potassium losses in the kidney, and at the time, strengthened our suspicion for proximal tubular damage and Fanconi syndrome.

Fanconi syndrome is a disorder of kidney tubules that causes

**Table 2.** Effects on Renal Function During Deferasirox Therapy as per Case Reports [2, 7-13]

| Case Report | Patient | Dose | Finding | Outcome |
|---|---|---|---|---|
| Rafat, et al. 2009[2] | 78 y/o M w/ chronic lymphocytic leukemia, sideroblastic anemia, and transfusion dependence. | 24mg/kg/d | Increase in Cr from 0.9 to 1.4 to 2.0, hypophosphatemia, metabolic acidosis, glycosuria. Diagnosis: Fanconi syndrome. | Drug was stopped and creatinine fell to 1.2. All features of proximal tubule dysfunction resolved. |
| Brosnahan, et al. 2008[7] | 62 y/o M w/ myelodysplastic syndrome and myeloproliferative disorder. | 2g/d | Increase in Cr from 1.6 to 2.2 to 3.0 and proteinuria. Biopsy showed acute interstitial nephritis. | Drug was stopped. Cr level returned to 1.3. |
| Yusuf, et al. 2008[8] | 43 y/o F w/ sickle cell disease, ESRD on peritoneal dialysis, and transfusion dependence. | 1.5g/d | Decrease in serum calcium from 8.0 to 5.9. Diagnosis: symptomatic hypocalcemia. | Drug was stopped and calcium normalized. Drug was then restarted; calcium again fell from 8.0 to 6.5. |
| Even-Or, et al. 2010[9] | 18 y/o M w/ pure red cell aplasia and transfusion dependence. | 20mg/kg/d | Increase in Cr from 0.6 to 1.07, glycosuria, hypokalemia, hypophosphatemia, phosphaturia, and aminoaciduria. Diagnosis: Fanconi syndrome. | Drug was stopped and electrolyte abnormalities resolved. Drug was then restarted and abnormalities reoccurred. |
| | 11 y/o F w/ B-thalassemia major and transfusion dependence. | 20mg/kg/d | Developed glycosuria, hypophosphatemia, proteinuria, phosphaturia, and amino-aciduria. Diagnosis: Fanconi syndrome. | Drug was stopped and both serum and urine labs normalized. |
| Grange, et al. 2010[10] | 77 y/o M w/ nonhereditary hemochromatosis | 1.5g/d | Developed increased Cr, hypokalemia, glycosuria, asthenia, anorexia, constipation, and epigastralgia. Diagnosis: Fanconi syndrome. | Drug was stopped and patient had complete resolution of symptoms and recovery of renal function. |
| Yew, et al. 2010[11] | 70 y/o M w/ porphyria cutanea tarda and multiple myeloma. | Not reported | Developed acute renal failure requiring dialysis. Biopsy showed tubulointerstitial nephritis. | Drug was stopped. Patient was started on dialysis and steroids. Creatinine returned to baseline. |
| Wei, et al. 2011[12] | 18 y/o M w/ B- thalassemia major and transfusion dependence. | 1375mg/d | Developed coma, hepatic dysfunction, thrombocytopenia, metabolic acidosis, elevated Cr, proteinuria and glycosuria. Diagnosis: Fanconi syndrome. | Drug was stopped and patient had full recovery. |
| Rheault, et al. 2011[13] | 7 y/o M w/ B-thalassemia major and transfusion dependence. | 0.5g/d | Developed nausea, anorexia, phosphaturia, aminoaciduria, glycosuria, hypokalemia, metabolic acidosis. Diagnosis: Fanconi syndrome. | Drug was stopped. Labs normalized. Drug was then restarted at lower dose. Labs again showed evidence of proximal tubule dysfunction. |
| | 8 y/o F adopted sibling of patient 1 also with B thalassemia major. | 0.5g/d | Developed elevated B2-microglobulin, microscopic hematuria, and proteinuria. | No treatment intervention. Continued to monitor. |

Abbreviations: y/o = year old; M = male; F = female; Cr = creatine

urinary loss of glucose, protein, potassium, phosphate, bicarbonate, and amino acids. Patients often present with generalized weakness, bone pain, and hypovolemia secondary to large volume urine loss. This is a rare disease with a limited number of etiologies. In children, cases are typically inherited; the most commonly associated diseases are cystinosis and Wilson's disease. In adults, etiologies include light chain disease such as multiple myeloma or amyloidosis, use of carbonic anhydrase inhibitors, heavy metal toxicity such as lead poisoning, and nephrotoxic drugs.[1] Our patient's ceruloplasmin was normal and he had no evidence of heavy metal toxicity. Upon review of his medications, ifosfamide and deferasirox were 2 drugs he had taken with links to proximal tubule injury. The patient did have trace glycosuria on his initial urinalysis in March 2011, which suggests a residual mild tubulopathy from ifosfamide as well. However, the progressive decline in renal function and full constellation of Fanconi syndrome suggests acute damage from deferasirox.

A review of the literature revealed less than a dozen case reports documenting significant renal dysfunction in the setting of deferasirox use. Injuries described include Fanconi syndrome, acute interstitial nephritis, calcium wasting, and acute renal failure (Table 2). Though the mechanism of kidney injury is unknown, a letter to the *American Journal of Kidney Diseases* in March 2010 from Dr Robert Hider suggests the nephrotoxicity of deferasirox is associated with the deferasirox-iron compound triple negative charge.[14] The negative charge traps the compound intracellularly, thus damaging the cell.

The history of ifosphamide and deferasirox use provided a good explanation for the patient's Fanconi syndrome. However, this did not explain the patient's progressive renal failure, so a biopsy was performed. Figure 1 is a silver stained section from our patient's biopsy at 400X magnification. The tubular epithelial cells have marked cytoplasmic vacuolization consistent with drug toxicity—similar to that reported in the animal studies in marmosets and rats that were administered oral deferasirox.[15]

Because the biopsies showed vacuolization and no evidence

of light chain deposition, no evidence of glomerular injury and no evidence of interstitial inflammation, and because evidence of renal injury coincided with the initiation of iron chelation therapy, deferasirox was left as the as the most likely explanation for both Fanconi syndrome and progressive renal failure. This is the first known case of Fanconi syndrome with biopsy-documented proximal tubulopathy in the setting of deferasirox use.

## CONCLUSION

This case report highlights the possibility of deferasirox-associated Fanconi syndrome and renal failure. The convenience of taking an oral medication is a great breakthrough in chelation therapy; however, it carries the risk of these rare side effects. Thus, we recommend monitoring of renal function with serial urinalyses, electrolyte levels, and creatinine levels during treatment.

Fanconi syndrome should be suspected in patients who present with low serum bicarbonate, potassium, and phosphorous levels in addition to glycosuria. All case reports thus far have demonstrated complete recovery of Fanconi syndrome and improvement in creatinine levels with cessation of deferasirox. Unfortunately, though our patient's renal function improved with cessation of therapy, he continues to require a significant amount of potassium and phosphorous supplementation daily.

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