Published in final edited form as:
J Pediatr Hematol Oncol. 2010 October ; 32(7): 525–526. doi:10.1097/MPH.0b013e3181ec0c4d.

Renal Fanconi Syndrome Secondary to Deferasirox: Where There is Smoke There is Fire

Michel Baum[1,2]

[1]Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas Dallas, Texas 75235-9063

[2]Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas Dallas, Texas 75235-9063

The kidney filters ~150 liters per day and reabsorbs 99% of this ultrafiltrate of plasma. The renal tubule is segmented and different portions of the nephron have selective roles in solute and volume reabsorption. The proximal tubule reabsorbs four-fifths of the filtered bicarbonate, two-thirds of the filtered chloride, and essentially all of the filtered glucose, amino acids, and phosphate. Thus, significant injury to the proximal tubule leads to volume depletion, metabolic acidosis, and hypophosphatemia. Hypokalemia is also a common manifestation as aldosterone levels are elevated due to volume depletion and there is increased delivery of sodium and bicarbonate to the distal nephron where sodium is reabsorbed causing a lumen negative potential leading to potassium secretion across an apical potassium channel. Hypomagnesemia is also a common feature of the Fanconi Syndrome.

Injury to the proximal tubule with the preservation of glomerular filtration results in the Fanconi syndrome. While there are many causes for the Fanconi syndrome including inherited diseases such as the cystinosis 1, there are a number of diseases and drugs causing the Fanconi Syndrome that may present to the Hematologist-Oncologist. The Fanconi syndrome can result from plasma cell dyscrasias, paraneoplastic syndromes and paroxysmal nocturnal hemoglobinuria; diseases that usually present outside of the pediatric age range. Pediatric Hematologist-Oncologists are more likely to see the Fanconi Syndrome secondary to cancer chemotherapeutic drugs such as iphosphamide, cisplatinum, 6-mercaptopurine, and Imatinib mesylate or secondary to drugs used to fight infections such as aminoglycosides, cidofovir, adefovir, and tenofovir. To this expanding list we can now add deferasirox to drugs that cause the Fanconi Syndrome 2.

The proximal tubule is a likely site of injury in view of the fact that it is the work horse of the nephron. A generalized proximal tubule disorder could be the result of inhibition of basolateral Na^+/K^+-ATPase activity, which lowers intracellular sodium providing a driving force for sodium dependent apical membrane transport. However, this would result in transport defects all along the nephron and a generalized tubulopathy. The selective proximal tubule injury is related to its tremendous requirement for fuel. Previous studies have shown that while Na^+/K^+-ATPase activity is intact if given exogenous ATP, the

Send Reprint Requests and Correspondence to: Michel Baum, M.D., Department of Pediatrics, U.T. Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390-9063, PH: (214) 648-3438, FAX: (214) 648-2034, Michel.Baum@UTSouthwestern.edu.

proximal tubule cellular ATP content is diminished in models of the Fanconi Syndrome 3. The cause for the toxicity of deferasirox may be due to its lipid solubility, allowing the drug to pass into cells and accumulate at high levels and bind to intracellular divalent and trivalent cations 4. Thus intracellular iron, that is necessary for oxidative phosphorylation and ATP production, may be critically deficient after deferasirox therapy 5.

There have been a few previous cases of deferasirox linked to the Fanconi syndrome 6-8. One can speculate that the few number of cases reported may be a coincidence, however this does not appear to be the case. In each of the cases reported to date and in the four cases reported in this issue of the Journal, all were reversible shortly after withdrawing deferasirox. Indeed, one patient was rechallenged with deferasirox with the recurrence of the Fanconi Syndrome 6. The Fanconi Syndrome is not the only renal problem caused by deferasirox as a rise in serum creatinine indicative of acute kidney injury was also noted in several cases 2;6-8. In the Phase III assessment of deferasirox, a small increase in serum creatinine was noted in noted in 38% of patients that either resolved spontaneously or decreased with a reduction in the dose of the drug 9.

The diagnosis of Fanconi syndrome is usually the result of evaluation of electrolytes and urinalysis in patients with vague constitutional symptoms of feeling unwell due to electrolyte deficiencies as noted below. Since patients have a generalized proximal tubule dysfunction there is usually glucosuria. However, since glucose is so avidly reabsorbed by the proximal tubule this can be a late manifestation of the Fanconi Syndrome. There are many causes of metabolic acidosis and hypokalemia, but most cases of hypophosphatemia are due to malnutrition or renal losses. A fractional excretion of phosphorus of greater than 15% in the face of hypophosphatemia is consistent with renal phosphate wasting.

The approach to the treatment of the Fanconi syndrome is to remove or limit the exposure of the offending agent, which is possible with deferasirox once the diagnosis is considered. However, the hypophosphatemia, hypomagnesemia, hypokalemia and metabolic acidosis can have devastating and even fatal consequences. Hypokalemia can result in nephrogenic diabetes insipidus, decreased bowel motility, muscle weakness or paralysis, cardiac arrhythmias, and a predisposition to rhabdomyolysis. Since magnesium is necessary for the release of parathyroid hormone and the action of parathyroid hormone on bone, hypomagnesemia can result in muscle spasticity. Hypomagnesemia can result in apathy, nausea, and if severe seizures and cardiac arrhythmias. Since phosphate is necessary for almost all metabolic processes, hypophosphatemia has a myriad of systemic effects including muscle weakness, altered mental status, seizures, hypoventilation, a decrease in cardiac output and a predisposition to rhabdomyolysis. Both chronic hypophosphatemia and metabolic acidosis can result in metabolic bone disease and poor growth. The treatment of Fanconi's syndrome, besides removing the toxic agent, is electrolyte replacement. However, one must be exceedingly careful in correcting these electrolyte problems. For example, correction of the acidosis by the administration of alkali before correction of the serum potassium will result in worsening of the hypokalemia that can result in paralysis, cardiac arrhythmias and death. Robust administration of calories in a hypophosphatemic patient can cause refeeding syndrome.

The extent of the nephrotoxicity of deferasirox is unclear because assessment of glomerular filtration rate was reliant on serum creatinine 9. Since one can donate a kidney and loose 50% of renal function without a substantive change in serum creatinine, a significant degree of renal injury must occur for there to be an increase in creatinine levels. In terms of the Fanconi syndrome, the growing number of cases and the fact that 4 cases are now reported out of 50 cases followed at one institution is a significant concern 2. In each of the cases to date, removal of the offending agent resulted in the resolution of the Fanconi Syndrome;

however it is not clear if prolonged unrecognized injury may cause chronic kidney injury. Clearly, one must be diligent in monitoring patients who are taking deferasirox.

Acknowledgments

Dr. Baum is supported by NIH grants DK41612, DK78596, and the O'Brien CenterP30DK079328.

Reference List

1. Moe, O.; Seldin, DW.; Baum, M. The Fanconi Syndrome. In: Lifton, R.; Somlo, S.; Giebisch, G., et al., editors. Genetic Diseases of the Kidney Burlington. Elsevier; MA: 2009. p. 141-60.
2. Yacobovich J, Stark P, Barzilai-Birenbaum S, Kraus I, Pazgal I, Yaniv I, Tamary H. Acquired proximal renal tubular dysfunction in B-thalassemia patients treated with deferasirox. J Pediatr Hematol Oncol. 2010 In Press.
3. Coor C, Salmon RF, Quigley R, et al. Role of adenosine triphosphate (ATP) and NaK ATPase in the inhibition of proximal tubule transport with intracellular cystine loading. J.Clin.Invest. 1991; 87:955–61. [PubMed: 1847941]
4. Hider RC. Charge states of deferasirox-ferric iron complexes. Am J Kidney Dis. 2010; 55:614–15. [PubMed: 20189051]
5. Oexle H, Gnaiger E, Weiss G. Iron-dependent changes in cellular energy metabolism: influence on citric acid cycle and oxidative phosphorylation. Biochim.Biophys.Acta. 1999; 1413:99–107. [PubMed: 10556622]
6. Even-Or E, Becker-Cohen R, Miskin H. Deferasirox treatment may be associated with reversible renal Fanconi syndrome. Am J Hematol. 2010; 85:132–34. [PubMed: 20052747]
7. Grange S, Bertrand DM, Guerrot D, et al. Acute renal failure and Fanconi syndrome due to deferasirox. Nephrol.Dial.Transplant. 2010
8. Rafat C, Fakhouri F, Ribeil JA, et al. Fanconi syndrome due to deferasirox. Am J Kidney Dis. 2009; 54:931–34. [PubMed: 19493602]
9. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006; 107:3455–62. [PubMed: 16352812]