



## A rare case of parental iron-induced persistent hypophosphatemia

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### ABSTRACT

We report a case of an African American woman who presented with fatigue, generalized weakness, and hypophosphatemia in the setting of a recent hospitalization for severe, symptomatic iron deficiency anemia requiring ferric carboxymaltose infusions. Parental iron is indicated in numerous clinical settings including chronic kidney disease, inflammatory bowel disease, and iron deficiency anemia. Ferric carboxymaltose is one of the most common forms of parental iron infusions used due to administration procedure and minimal reported side effects. The most common side effect reported is a transient decrease in serum phosphate. This case highlights the necessity of monitoring serum phosphate in the setting of parental iron infusions, especially ferric carboxymaltose, and when severe hypophosphatemia occurs management includes intravenous phosphorous and calcitriol.

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## 1. Introduction

Parental iron is indicated in numerous clinical settings including chronic kidney disease, inflammatory bowel disease, and iron deficiency anemia. A transient decrease in serum phosphate is the most common side effect; however, there have been few accounts of severe, persistent hypophosphatemia reported. Symptoms of hypophosphatemia range from asymptomatic (when mild) to arthralgia, osteodynia, altered mental status, and seizures. We report a case that illustrates the importance of monitoring serum phosphate in the setting of parental iron infusions.

## 2. Case presentation

A 32-year-old woman with a past medical history of mixed connective tissue disorder, rheumatoid arthritis, systemic lupus erythematosus, iron deficiency anemia, and remote history of pulmonary embolism and cerebrovascular accident was hospitalized with fatigue, generalized weakness, and severe hypophosphatemia. Four weeks prior to hospitalization the patient began intravenous ferric carboxymaltose infusions for symptomatic iron deficiency anemia.

At the time of her first infusion, serum phosphate was 3.6 [ref: 2.5–4.5] mg/dL. One week later, the patient was hospitalized for fatigue, weakness, and lightheadedness. Her symptoms were attributed to a urinary tract infection. Interestingly, serum phosphate was noted to be 1 mg/dL and was repleted with 21 mmol of potassium phosphate. The patient's serum phosphate level was not reassessed until hospitalization, just prior to her third

scheduled ferric carboxymaltose infusion, and was <1 mg/dL. The patient's severe hypophosphatemia was corrected with a total of intravenous [IV] sodium phosphate 60 mmol, IV potassium phosphate 151 mmol, oral monobasic and dibasic sodium and potassium phosphate 3,750 mg, and calcitriol 0.25 mcg daily over the course of 5 days.

The etiology of her severe hypophosphatemia was attributed to ferric carboxymaltose infusions, which were discontinued prior to discharge. Discontinuation of intravenous iron infusion and phosphate replacement greatly improved her fatigue and generalized weakness.

## 3. Discussion

Parental iron preparations are indicated in cases of severe iron-deficient anemia, of which iron-carbohydrate complexes (ferric carboxymaltose and iron isomaltoside) are most common. Often these preparations are utilized first due to administration procedure, short length of infusion (15 min), and low risk of allergic reactions as demonstrated in clinical trials [1]. The most commonly noted side effect during clinical trials was a transient reduction in serum phosphate in patients with inflammatory bowel disease [1]. The lowest concentration of serum phosphate was noted to be 2 weeks after completing a parental iron infusion with normalization within 4 to 12 weeks [1,2]. Unfortunately, in the setting of serial iron infusions, hypophosphatemia may be persistent.

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Normal plasma phosphate concentration is defined as 2.5–4.5 mg/dL. Hypophosphatemia is a common finding in hospitalized patients, for which there is a wide range of causes but ultimately involves one or more of the following: decreased gastrointestinal absorption, increased renal excretion, and translocation of phosphate from intracellular to extracellular space. Various etiologies include refeeding syndrome, alcohol withdrawal, toxic shock syndrome, vitamin D-deficient rickets, McCune-Albright syndrome, X-linked hypophosphatemia, etc. [3]. Symptomatology of hypophosphatemia is dependent on the severity of the deficiency and can include severe cardiomyopathy with reduced cardiac output, hyperinsulinemia, rhabdomyolysis, hematologic abnormalities including thrombocytopenia and hemolysis, and neurologic abnormalities including ataxia, seizures, and coma [3].

A typical daily American diet contains approximately 1 g of phosphate, of which 700 mg is absorbed, and 300 mg is excreted. Phosphate balance is dependent upon gastrointestinal absorption and renal excretion and reabsorption, both of which involve the sodium-phosphate cotransporter system. The sodium-phosphate cotransporter NaPi-IIb, along the intestinal brush border epithelial membrane is upregulated by a diet low in phosphate and 1,25-dihydroxyvitamin D3 [3]. Renal phosphate excretion is dependent on the NaPi-IIa and NaPi-IIc cotransporters, which is inhibited by fibroblast growth factor 23 (FGF 23) [4].

FGF 23 is a hormone excreted by the skeletal osteoclast in response to serum phosphate levels to regulate vitamin D and serum phosphate levels. FGF 23 acts to inhibit expression of the sodium-phosphate transporters, NaPi-IIa and NaPi-IIc, in the renal system, which results in increased phosphate excretion [4].

Following iron-carbohydrate complex infusions, for instance ferric carboxymaltose, there is an increase of intact, biologically active FGF 23. This results in significant renal phosphate wasting and reduced renal reabsorption. There have been several isolated case reports with iron-carbohydrate complex induced severe hypophosphatemia. Overall the risk of severe, persistent hypophosphatemia may be more likely following ferric carboxymaltose administration [4,5]. Cessation of these infusions alongside the administration of phosphate supplementation and calcitriol has shown to be effective management.



## 4. Conclusion

Hypophosphatemia is a common finding in hospitalized patients. Several common causes include reduced oral intake, redistribution of phosphate, iatrogenic, and hyperparathyroidism [4]. One notable iatrogenic agent is parental iron-carbohydrate complexes and the risk of developing severe persistent hypophosphatemia may be increased with ferric carboxymaltose administration. Ferric carboxymaltose inhibits FGF 23 degradation resulting in renal phosphate wasting by inhibition of the sodium-phosphate cotransporters, NaPi-IIa and NaPi-IIc. Ferric carboxymaltose is a favored parental iron agent due to short administration time, procedure, and infrequent post-infusion side effects. It is imperative physicians monitor serum phosphate in the setting of parental iron infusions and are aware of the potential symptoms and complications of hypophosphatemia. Furthermore, when severe, persistent hypophosphatemia occurs it should be treated with discontinuation of parental iron infusions and serial phosphate supplement infusions and calcitriol.

## Disclosure Statement

No potential conflict of interest was reported by the authors.

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## References

- [1] Schaefer, Benedikt et al. "Choice of High-Dose Intravenous Iron Preparation Determines Hypophosphatemia Risk." *PLoS onevol.* 11,12 e0167146. 1 Dec. 2016, doi:10.1371/journal.pone.0167146.
- [2] Anand G, Schmid C. Severe hypophosphatemia after intravenous iron administration. *BMJ Case Rep* [Internet]. 2017 Mar 13 [cited 2019 Nov 10];2017:bcr2016219160.
- [3] Coffman TM, Schrier RW. *Schrier's diseases of the kidney.* [Electronic resource] [Internet]. Philadelphia, PA, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013 [cited 2020 Jan 3].
- [4] Fang W (1,2), Bloom S (1,2), Garg M (1,2), et al. Symptomatic severe hypophosphatemia after intravenous ferric carboxymaltose. *JGH Open* [Internet]. 2019 Nov 10;3(5):438–440.
- [5] Shimizu Y (1), Okamoto T (1), Suzuki H (1), et al. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide. Another form of FGF23-related hypophosphatemia. *Bone* [Internet]. 2019 Nov 10;45(4):814–816.