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Case Report

Unveiling the Unexpected: Notable Side Effect of IV Ferric Carboxymaltose - A Case Report

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Abstract

Introduction: Anemia, affecting 1.62 billion globally, is commonly due to iron deficiency. Treatments include oral supplements, intravenous (IV) infusions, and blood transfusions, with ferric Carboxymaltose (FCM) often preferred for IV infusions due to its effectiveness. However, FCM can cause hypophosphatemia by increasing fibroblast growth factor 23 (FGF23), leading to higher renal phosphate excretion and lower serum phosphate levels.

Case Report: A 48-year-old woman with Type 2 diabetes and iron deficiency anemia chose FCM for treatment. Despite an initial improvement in hemoglobin levels, she developed severe hypophosphatemia two weeks post-infusion, presenting with muscle pain and fatigue. Labarotory tests confirmed low phosphate levels. Treatment with oral phosphate and calcitriol improved her symptoms over a month.

Discussion: Iron deficiency anemia treatment varies based on severity and patient needs. FCM offers rapid iron correction with a low risk of anaphylactic reactions but has a significant side effect of hypophosphatemia. This occurs due to increased Fibroblast Growth Factor 23 levels, leading to increased phosphate excretion and reduced calcitriol levels, further decreasing phosphate absorption.

Conclusion: To prevent severe hypophosphatemia in patients receiving FCM, it is crucial to monitor and manage serum phosphate, calcium, and vitamin D levels, especially in at-risk individuals. Proactive supplementation and regular follow-up are essential for early detection and treatment of deficiencies.

Keywords: Ferric Carboxymaltose; Hypophosphatemia; Fibroblast Growth Factor-23; Anemia; Vitamin D

Abbreviations

IV: Intravenous; FCM: Ferric Carboxymaltose; IDA: Iron Deficiency Anemia; FGF 23: Fibroblast Growth Factor 23; PTH: Parathyroid Hormone

Introduction

Anemia, a condition that affects the oxygen-carrying capacity of blood, impacts 1.62 billion people worldwide. The causes of anemia are numerous and can include nutritional deficiencies such as iron deficiency or vitamin B12 deficiency, blood loss from conditions like gastrointestinal bleeding, heavy menstrual bleeding, or trauma and bone marrow disorders such as aplastic anemia, myelodysplastic syndromes, and leukemia. Among the various causes of anemia, iron deficiency anemia (IDA) is the most common [1]. Depending on the severity, IDA can be managed by oral supplementation, intravenous (IV) infusion of iron formulations, or blood trans-

fusions. Among the different injectable iron formulations, Ferric Carboxymaltose (FCM) has been shown to cause greater resolution of iron deficiency compared to intravenous iron sucrose or oral ferric maltose [2].

Some studies have suggested that FCM inhibits the Fibroblast growth factor 23 (FGF23) degradation and increases its serum level. FGF23 and Parathyroid hormone (PTH) play important roles in the regulation of absorption, metabolism, and renal excretion of Phosphate. Absorption of phosphate takes place in the small intestine in the presence of 1,25, OH vitamin D3. When increased FGF 23 is present in circulation, it increases renal excretion of phosphate and decreases its serum level leading to hypophosphatemia [2]. Here, we present a case of a patient with iron deficiency anemia and vitamin D deficiency who developed severe hypophosphatemia after intravenous injection of FCM.

Case Report

A 48-year-old woman with Type 2 diabetes, managed with regular oral antidiabetic medications, visited the outpatient department with complaints of easy fatigue and effort intolerance over a period of past three months. She had no notable history of blood loss, worm infestation, or Non-Steroidal Anti-Inflammatory Drug use. Her general and systemic examinations were normal except for pallor.

Her complete hemogram revealed microcytic and hypochromic anemia with normal reticulocyte count without any features of hemolysis. Corelating with her biochemical profile of low serum iron and low serum ferritin, she was diagnosed as a case of Iron deficiency anemia (IDA) (Table 1). Liver and kidney function tests were normal. An upper gastrointestinal endoscopy revealed gastric erosions.

Given her symptomatic anemia, she was offered the choice between a blood transfusion or an intravenous iron infusion (either IV iron sucrose or IV FCM). She opted for the FCM injection and received two doses of 750 mg in 300 ml of normal saline daily for two days following intradermal sensitivity testing. She experienced no immediate complications during or after the infusions.

However, two weeks later, she returned with similar complaints of severe muscle pain and increased fatigue, which had worsened from the last presentation. Her daughter noted she was more irritable than usual. She did not exhibit any muscle weakness, maintaining full strength in all four limbs.

Repeat blood tests showed her hemoglobin had increased to 9.3 g/dl, but she had hypophosphatemia, her serum phosphate had dropped to 0.8 mg/dl. Her random blood sugar was 231 mg/dl, and electrolytes, liver and kidney function, creatine kinase (CK), and CK-MB were normal. Fasting cortisol was also normal, and her parathormone level was within normal limit (Table 1).

Parameters	Reference range	Day 1	After 2 weeks
Hematologic Parameters			
Hemoglobin (gm%)	13-17	7.6	9.3
TC (x10^{3}µL)	4-10	6.8	6.4
Neutrophil (%)	40-70	68	66
Lymphocyte (x10^{3}µL)	20-40	22	22
MCV (femtoliter)	81-100	63	76
MCH (picogram)	27-32	18	20
MCHC (g/dL)	31.5-34.5	26	30
Platelet count (x10^{3}µL)	150-410	210	311
ESR (mm/hour)	0-20	23	18
Corrected reticulocyte count	0.5-1.5	1.1	1.2
Peripheral smear	Microcytic hypochromic anemia with normal platelet and leucocyte count		
Coomb's test	Negative for both DCT and ICT		
Biochemical Parameters			
RBS (mg/dL)	70-140	207	231
Urea (mg/dL)	15-37	18	17
Creatinine (mg/dL)	0.50-1.4	0.7	0.6
TBIL (mg/dL)	1.3-1.5	1.4	1.5
DBIL (mg/dL)	0-0.3	0.4	0.5
Albumin (g/dL)	3.5-5	4.2	4.2
TSH (mIU/L)	0.40-4.05	3.76	
Iron (mcg/dL)	60-170	16	40
Ferritin (ng/ml)	13-150	05	13
Vitamin B12 (pg/ml)	160-950	446	526

Transferrin Saturation (%)	15-50	13	15
TIBC (mcg/dL)	240-450	685	584
Uric acid (mg/dL)	2.5-6.2	6.0	5.4
LDH (U/L)	120-246	168	152
Serum Calcium (mg/dL)	8.4-10.2	9.1	9.6
Serum Phosphorus (mg/dL)	2.5-4.5	2.4	0.8
Serum Vitamin D3 (ng/ml)	30-100	N/A	21
Serum PTH (pmol/L)	1.6-6.9	N/A	4.6
Urine Analysis	Straw-coloured, Protein/Albumin: Nil, Sugar: Nil, RBCs: Nil, No casts		

Table 1: Hematological parameters and Urine analysis.
Abbreviation: TC: Total count; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; ESR: Erythrocyte sedimentation rate; RBS: Random blood sugar; TBIL: Total Bilirubin; DBIL: Direct Bilirubin; qCRP: Quantitative C-reactive protein; TSH: Thyroid function test; LDH: Lactate dehydrogenase; DCT: Direct Coomb's test; ICT: Indirect Coomb's test; RBC: Red Blood cells; N/A: Not available.

She was started on oral phosphate replacement with sodium phosphate 500 mg four times a day and oral calcitriol 0.25 mcg daily. Despite starting treatment, her symptoms persisted, though less severely, for nearly a month. Her phosphate levels were monitored regularly, and she continued the medications until her phosphate levels normalized.

Results and Discussion

IDA can be managed through several approaches, depending on the severity of the condition. Oral iron supplementation such as ferrous sulfate, ferrous gluconate, and ferrous fumarate are non-invasive, convenient, and generally effective for mild to moderate cases. However, these drugs can cause gastrointestinal side effects (nausea, vomiting, and constipation), require adequate absorption, and may take several weeks to months to correct anemia. IV Iron Infusions like FCM, Iron sucrose, and Iron dextran allow for rapid correction of iron levels, useful in cases where oral iron is ineffective or not tolerated, or in severe anemia. IV iron infusions require medical supervision, risk of infusion reactions, cost, and access to healthcare facilities. Blood transfusions is indicated in patients with severe anemia and having significant symptoms (e.g., fatigue, shortness of breath and chest pain) or in emergencies. It has the advantage of an immediate increase in hemoglobin levels. The choice of treatment depends on the patient's individual needs, severity of anemia, underlying cause and response to initial therapy [2].

FCM is a colloidal Iron hydroxide complexed with carboxymaltose, a carbohydrate polymer. This configuration allows controlled delivery of iron to the reticuloendothelial system's cells and subsequently to iron-binding proteins such as ferritin and transferrin. One of the key benefits of FCM is that it minimizes the risk of releasing large amounts of ionic iron into the serum. Additionally, FCM is an iron dextran-free product, which enhances its stability and reduces its immunogenic potential, thereby lowering the risk of anaphylactic reactions [3].

One increasingly reported side effect of FCM is hypophosphatemia, which can cause a variety of symptoms. These symptoms range from myalgia, asthenia, myopathy, osteomalacia, bone pain, and fractures to fatigue, confusion, seizures, and even coma. The incidence of hypophosphatemia with FCM varies widely, with reported rates ranging from 0% to 92% [4].

FCM can cause hypophosphatemia through a series of physiological processes involving the regulation of phosphate metabolism. FCM administration leads to an increase in the levels of intact fibroblast growth factor 23 (FGF23). FGF23 is a hormone produced by osteocytes and osteoblasts in bones, which plays a critical role in regulating phosphate and vitamin D metabolism. Elevated FGF23 levels result in increased urinary excretion of phosphate. FGF23 reduces the expression of sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc) in the renal proximal tubules, leading to decreased reabsorption of phosphate and thus increased phosphate excretion. FGF23 also suppresses the activity of 1α-hydroxylase in the kidneys, which is responsible for converting 25-hydroxyvitamin D into its active form, calcitriol (1,25-dihydroxyvitamin D). Reduced calcitriol levels decrease intestinal absorption of phosphate and calcium [5].

Pre-existing problems in phosphate homeostasis can indeed increase the risk of developing symptomatic hypophosphatemia fol-

lowing FCM infusion. These pre-existing issues include low levels of vitamin D, calcium, and phosphate [6].

Conclusion

- It is crucial to monitor serum levels of phosphate, calcium, and vitamin D before and after FCM administration, especially in patients with known deficiencies or risk factors.
- Supplementation: Proactive supplementation of phosphate, vitamin D, and calcium may be necessary in at-risk patients to prevent or mitigate the development of symptomatic hypophosphatemia.
- Follow-Up: Regular follow-up and monitoring of patients receiving FCM can help identify and address any emerging deficiencies early, preventing severe complications.

Understanding these pre-existing conditions and their impact on phosphate homeostasis is essential for healthcare providers to manage and mitigate the potential side effects of FCM infusions effectively.

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Conflict of Interest

Authors declare no conflict of interest.

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