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Hypophosphatemia induced encephalopathy after intravenous iron carboxymaltase administration – A rare and important complication

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Abstract

Recently, intravenous iron supplements has become increasingly popular because it allows administration of large quantity of iron dosage with simple infusion and is more effective in raising the hemoglobin levels and have less drug-related side effects as compared to oral iron supplementation. Multiple IV formulations of iron are available. However, there have been reports of transient asymptomatic hypophosphatemia with its use. We report here a patient with iron deficiency anemia secondary to menorrhagia, who presented with confusion, disorientation, muscle cramps and severe fatigue 3 weeks following intravenous ferric carboxymaltase from hypophosphatemia.

Keywords: Encephalopathy, IV ferric carboxymaltase, hypophosphatemia, intravenous iron administration, adverse effects of IV iron infusion,

INTRODUCTION

Iron deficiency is one of the most common causes of anemia. Symptoms of anemia are often relieved by iron supplements. Currently, intravenous iron supplements allow administration of larger quantity of iron. These supplements are easy to administer, can lead to faster increase of hemoglobin levels and are well tolerated. However, one should also be aware about their potential adverse events like hypophosphatemia, the common symptoms are fatigue, bone pain, malaise, dyspnea and loss of appetite.

The common causes of hypophosphatemia include chronic kidney disease, hyperparathyroidism, vitamin D deficiency, nutritional deficiencies, as well as adverse effects of medications such as IV iron preparations. Other than symptoms mentioned above, serious complications of prolonged hypophosphatemia may include seizures, coma, rhabdomyolysis and cardiac arrhythmia. Hypophosphatemia is defined as levels of phosphate below 2.5 mg/dl. Levels below 1 mg/dl are deemed severe. We present here a woman who developed encephalopathy from hypophosphatemia as adverse effect of IV iron (ferric carboxymaltase) treatment.

CASE REPORT

A 34 year old woman who was a medical practitioner had normal birth history and developmental milestones. She was diagnosed with iron deficiency anemia due to menorrhagia with HB 8.0 gems/dl, serum iron 4 micromole/L, serum ferritin 50microgm/L. She was given many trials of oral iron therapy, but was intolerant to the oral iron. As such, she was given intravenous 1500 mg of ferric carboxymaltase in divided dosages separated by 10 days. The infusion was uneventful and no side effects were reported during the therapy. She had no significant past medical history other than the chronic iron deficiency anemia. She previously tolerated IV dextran iron in the past. This was the first occasion she received IV iron ferric carboxymaltase. Five days after the last infusion, she felt that her ability to think was impaired, there was an unusual delay in processing her thoughts and comprehending the events. Due to the nature of her work, this change in concentration and cognition was of concern to her. She had difficulty in recollecting the recent events like what she had for breakfast or what did a day prior. She also noted severe fatigue, lethargy and frequent leg cramps in the last two days. On examination, she was disoriented in terms of month and year which was most unusual

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for her occupation background. She had no flaps, tremors, motor or sensory abnormalities.

Further investigations showed serum phosphate of 1.4 mg/dl (normal 2.7 to 4.5 mg/dl), SGPT 385 IU/L (normal <32 IU/L), SGOT 174 (normal <33 IU/L), 25 OH vitamin D 12.58 mg/ml (deficiency below 20ng/ml). The fractional excretion of phosphate was 44.3%. Other investigations include serum calcium, magnesium, parathyroid hormone, alkaline phosphate, creatinine kinase, renal function test, serum ammonia were normal. The Hemoglobin was 10.8 gm/dl. The MRI brain, EEG, ECG, echocardiogram were all normal. CSF examination was planned depending on the response to supplementation of phosphates to correct the hypophosphatemia.

The cause of confusion was attributed to hypophosphatemia. Intravenous phosphate therapy was avoided in view of danger of cardiac arrhythmia. IV or oral phosphate in other form could not be procured from any pharmacy in the city due to concurrent strike in the pharmaceutical distribution network. She was given dietary phosphate replacement therapy, bed rest, fat free diet, multi vitamins and for the correction of phosphate, oral sodium phosphate enema (100 ml of enema contains 8 gms of sod phosphate and 10 gms of phsophate) 8 ml a day in divided dose. Vitamin D was gradually corrected with 60,000 IU weekly supplementation. The phosphate level was repeated weekly and the values were persistently below 1.5 mg/dl. The phosphate dosage was increased to 12 ml daily in divided dosages however there was edema of feet. It was thought to be due to excess sodium content in the enema, hence the dosage was adjusted back to 8 ml daily.

The confusion started to improve after a week. The muscle pain and cramps, and tiredness also improved. The levels of phosphate were checked weekly. The values remained low up to 3 months. The elevated SGPT/SGOT normalized in 3 weeks.

DISCUSSION

There have been many studies have showing the superiority of intravenous versus oral iron therapy.[1-3] Hypophosphatemia is known after ferric carboxymaltase treatment particularly in malnourished individuals and patients with endocrine dysfunction.[4] We reported here a young woman with iron deficiency anemia who developed adverse effects from hypophosphatemia from administration of IV carboxymaltase. Many varied systemic adverse effects of the IV carboxymaltase have been noted in literature.[4] Our patient presented with central nervous system complication of mental confusion which is rare.

Phosphate homeostasis is complex with bone-renal-endocrine axis playing an important role. Serum parathyroid hormone, vitamin D, and fibroblast growth factor (FGF)23 are other factors that are closely interlinked to phosphate metabolism. Renal phosphate excretion is regulated mainly by parathyroid hormone and FGF23, which are both phosphaturic hormones.[5-7] Studies have shown that hypophosphatemia induced by intravenous iron is mediated by increased levels of FGF23.[8] Recent studies suggest that iron deficiency stimulates FGF23 transcription in osteocytes, after which excess FGF23 is cleaved within the osteocytes into inactive C-terminal FGF23 (c-FGF23) giving rise also to a stable active intact i-FGF23. Administration of ferric carboxymaltase appears to affect the balance by inhibiting the cleavage of i-FGF23. Hypophosphatemia occurs due to the phosphaturic action of FGF23.[9,10]

Hypophosphatemia is observed in about 3.8% of cases of chronic renal disease administered intravenous iron carboxymaltose and up to 70% in patients with gynecological problems. As patients with chronic renal disease already have restricted renal excretion of phosphate and up regulated levels of FGF23, a further increase in FGF23 will not have a profound effect on phosphate excretion while for patients with normal renal function excessive phosphaturia causes hypophosphatemia.[11]

In conclusion, intravenous iron preparations are not devoid of adverse effect. The present case showed that it can rarely result in hypophosphatemia manifesting as confusion and disorientation. It is possible that mild confusion or alteration of cognition/memory may be missed and the complication under-reported. Our patient also showed that in case of non-availability of oral phosphate salts to replace the phosphate loss, one can consider sodium phosphate enema to correct the hypophosphatemia.

REFERENCES

1. Charytan C, Qunibi W, Baile GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract* 2005;100:55-62.
2. Krafft A, Perewusnyk G, Hanseler E, Quack K, Huch R, Breymann C. Effect of postpartum iron supplementation on red cell and iron parameters in non-anaemic iron-deficient women: a randomised placebo-controlled study. *Int J Obstet Gynaecol* 2005;112:445-50.

3. Moore RA, Gaskell H, Rose P, Allan J. Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. *BMC Blood Disord* 2011;11:4.
4. Blazevic A, Hunze J, Boots JM. Severe hypophosphetemia after intravenous iron administration. *J Med Netherlands* 2014;72(1):49-53.
5. Haussler MR, Whitfield GK, Kaneko I, *et al*. The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. *Rev Endocr Metab Disord* 2012;13:57-69.
6. Tiosano D. Fibroblast growth factor-23 and phosphorus metabolism. *Endo Dev* 2011;21:67-77.
7. Bergwitz C, Jüppner H. Regulation of Phosphate Homeostasis by PTH, Vitamin D, and FGF23. *Ann Rev Med* 2010;61:91-104.
8. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG. FGF23elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. *J Clin Endocrinol Metab* 2009;94:2332-7.
9. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res* 2013; 28(8):1793-803..
10. Hussain I, Bhoyroo J, Butcher A, Koch TA, He A, Bregman DB. Direct comparison of the safety and efficacy of ferric carboxymaltose versus iron dextran in patients with iron deficiency anemia. *Anemia* 2013; 2013:169107.
11. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant* 2011;26:1599-607.