

# Severe hypophosphataemia after intravenous iron administration

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## ABSTRACT

Currently, in many centres, intravenous administration of iron is becoming increasingly popular because of higher efficacy and decreased side effects, mainly gastrointestinal, compared with oral iron therapy. Studies of intravenous ferric carboxymaltose administration in the postpartum setting and in patients with non-dialysis-dependent chronic kidney disease revealed a decrease in serum phosphate levels that was generally asymptomatic and transient.

Here, we report four cases of severe and symptomatic hypophosphataemia after intravenous iron administration. All patients received this as therapy for iron deficiency anaemia due to heavy menstrual bleeding. In most cases, a pre-existent disorder in the phosphate homeostasis existed, such as a secondary (cases 3 and 4) or tertiary hyperparathyroidism (case 1). However, in the second case there were no risk factors for a dysregulation of the phosphate homeostasis.

Based on these findings, we conclude that severe and symptomatic hypophosphatemia can occur as a side effect of intravenous iron administration and can persist for months after administration. Especially patients with low phosphate levels prior to therapy due to concomitant disorders in phosphate homeostasis (e.g. hyperparathyroidism, vitamin D deficiency) are at risk.

## KEYWORDS

Adverse effects, ferric compounds, hypophosphatemia, intravenous iron administration/supplementation

## INTRODUCTION

Iron deficiency is one of the most common causes of anaemia and is frequently encountered in patients with chronic kidney disease. Besides investigating the cause

### What was known on this topic?

Intravenous iron supplements are highly effective in treating iron deficiency anaemia. Besides a transient, asymptomatic hypophosphataemia, there are few adverse effects of these intravenous preparations compared with oral iron supplements.

### What does this add?

This article emphasises the importance of determining pre-existent disorders in phosphate homeostasis and continuous monitoring of serum phosphate levels after intravenous ferric carboxymaltose administration as the provoked hypophosphataemia can be severe, prolonged and potentially life-threatening.

of the deficiency, symptoms can be relieved by iron supplements, which can be either orally or intravenously administered. Oral iron supplementation is often poorly tolerated due to a high rate of gastrointestinal side effects, which leads to dose reduction or non-adherence to treatment.<sup>1-3</sup> Recently, intravenous iron supplements were developed that allow administration of large amounts of iron by one simple infusion. These iron supplements are more effective in achieving haemoglobin level increases and have less drug-related adverse effects.<sup>4</sup>

However, some studies of intravenous ferric carboxymaltose administration reported a decrease in serum phosphate levels. The induced hypophosphataemia was generally asymptomatic and transient.<sup>5-8</sup> In non-dialysis dependent chronic kidney patients, serum phosphate levels decreased in 3.8% of the patients receiving intravenous iron supplementation and did not reach a clinically important level.<sup>8</sup> However, in this paper it is demonstrated that a severe and potentially

life-threatening hypophosphataemia can be provoked by intravenous administration of iron supplements.

## CASE REPORT

### Case 1

A 45-year-old female of Asian origin received an unrelated living donor kidney allograft in May 2008 for end-stage renal failure due to diabetes mellitus type I. The postoperative course was complicated by a delayed graft function. Four years later, she has a good transplant function (estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m<sup>2</sup>) on a dual immunosuppressive regimen of tacrolimus (trough levels 5.5-10.5 µg/l) and mycophenolate mofetil (500 mg twice daily) and adequate glycaemic control with a basal-bolus insulin regimen (HbA<sub>1c</sub> 55 mmol/mmol). To treat the vitamin D deficiency, she received colecalciferol 400 IE, which resulted in sufficient 25(OH)vitamin D levels (78 nmol/l, normal 50-150 nmol/l). However, the pre-transplant secondary hyperparathyroidism did not resolve completely over time with serum parathyroid hormone (PTH) levels remaining around 12.0 pmol/l (normal 1.0-8.0 pmol/l) and near-normal serum phosphate (P) levels between 1.37 and 0.70 mmol/l (normal 0.80-1.40 mmol/l). Furthermore, mild systolic hypertension remained which was treated with a combination of amlodipine 10 mg once daily and irbesartan 150 mg twice daily.

Due to a benign endometrial polyp, the patient suffered from heavy menstrual bleeding which led to the development of iron deficiency anaemia. Laboratory findings were: Hb 6.0 mmol/l (normal 7.5-10.0 mmol/l), serum iron 4 µmol/l (normal 10-25 µmol/l), serum transferrin 84 µmolFe/l (normal 35-65 µmolFe/l), serum iron saturation 5% (normal 20-45%), serum ferritin 5 µg/l (normal 8-252 µg/l). As oral iron supplements caused significant gastrointestinal side effects, she received a single infusion of 1000 mg ferric carboxymaltose (Ferinject®, Vifor Nederland BV, the Netherlands). Eight days after initiating therapy, the patient developed generalised weakness and nausea. A deep hypophosphataemia was diagnosed (P 0.25 mmol/l) and inappropriate phosphaturia. The fractional excretion of phosphate was 59%; with hypophosphataemia it should be below 5%. There were no cardiopulmonary or haematological manifestations. The patient was admitted to hospital and received 40 ml sodium glycerophosphate intravenously (1 ml = 1 mmol P, Glycophos®, Fresenius Kabi Nederland BV, the Netherlands). Forty-eight hours later, the serum phosphate level rose to 0.43 mmol/l and her clinical condition improved rapidly. She was discharged with instructions to continue oral phosphate supplementation by sodium glycerophosphate 20 ml three times a day. Seventy-two hours after discharge, the patient returned to the emergency department presenting with vertigo, nausea, diarrhoea, general weakness and

tingling in both hands. Again, profound hypophosphataemia (P 0.17 mmol/l) and continued inappropriate phosphate fractional excretion of 33.3% were found. Moreover, plasma levels of fibroblast growth factor 23 (FGF23) were elevated at 202 RU/ml (normal <125 RU/ml). The patient was re-admitted to the hospital for short-term intravenous phosphate repletion, sodium glycerophosphate 20 ml twice daily, and within one day the serum phosphate level rose to 0.55 mmol/l. As the symptomatic hypophosphataemia resolved, treatment was continued with oral phosphate repletion (1 ml = 67 mg P), 20 ml three times a day. The patient was discharged with stable serum phosphate levels and within six weeks oral phosphate repletion was ceased. On subsequent controls, the serum phosphate levels remained stable within the normal range.

### Case 2

A 42-year-old Caucasian female with known systemic lupus erythematosus since 1998 developed iron deficiency anaemia (Hb 7.4 mmol/l, serum iron 5 µmol/l, serum transferrin 68 µmolFe/l, serum ferritin 15 µg/l) due to heavy menstrual bleeding, while on anticoagulant therapy consisting of calcium carbasalate and acenocoumarol for antiphospholipid syndrome and repeated cerebrovascular accidents. On ultrasound, a persistent ovarian follicle and endometrial hyperplasia were diagnosed. Initially, oral iron supplements were prescribed to treat the iron deficiency anaemia. However, the patient developed profound side effects that led to discontinuation of oral treatment and subsequent administration of three infusions of 1000 mg ferric carboxymaltose with a six-week interval. Three days after the last infusion, the patient was diagnosed with deep hypophosphataemia (P 0.32 mmol/l) and inadequate fractional excretion of phosphate (12.4%). Symptoms attributable to hypophosphataemia were not present. Additional laboratory findings revealed normal values of serum parathyroid hormone (4.92 pmol/l) and 25(OH) vitamin D (97 nmol/l) and resolved anaemia (Hb 8.6 mmol/l). The patient was advised to increase her dietary phosphate intake by increasing the intake of protein-enriched meals and the phosphate levels were restored to normal levels within four weeks. However, due to continued heavy menstrual bleeding, the iron deficiency anaemia recurred (Hb 4.5 mmol/l). Upon this, the patient was treated with a single infusion of 100 mg iron sucrose (Venofer®, Vifor Nederland BV, the Netherlands). After eight days, the patient once more developed a deep, although again asymptomatic, hypophosphataemia (0.33 mmol/l), which was resolved in a similar way by increasing the dietary intake of phosphate.

### Case 3

A 33-year-old Hindu female underwent a laparoscopic Roux-Y gastric bypass in 2010 on account of obesity

(body mass index 44 kg/m<sup>2</sup>). The postoperative course was complicated by pneumonia, which was treated with amoxicillin-clavulate and ciprofloxacin, and one year later she underwent a laparoscopic cholecystectomy because of symptomatic gallstones. During the following two years, she lost 55 kg in weight. In February 2012, she developed anaemia due to heavy menstrual bleeding (Hb 5.8 mmol/l, MCV 72 fl, ferritin 2 µg/l, transferrin saturation 5%). In addition, vitamin D deficiency (25(OH) vitamin D 13 nmol/l) and secondary hyperparathyroidism (PTH 12.8 pmol/l) were diagnosed. She was treated for three months with sustained-release ferrous sulphate 287 mg once daily, calcium 1000 mg and colecalciferol 800 IU. Seven months later, she presented to the internal medicine outpatient clinic with persisting anaemia (Hb 5.2 mmol/l, MCV 64 fl, ferritin 1 µg/l, transferrin saturation 1%). The vitamin D deficiency and hyperparathyroidism were also still present (25(OH) vitamin D 28 nmol/l, PTH 16.7 pmol/l). In addition, she had vitamin B<sub>12</sub> deficiency (vitamin B<sub>12</sub> <111 pmol/l, normal 142-725 pmol/l). Her renal function was good with an eGFR above 90 ml/min/1.73 m<sup>2</sup>. The persistent iron deficiency anaemia was treated with two infusions of 1000 mg ferric carboxymaltose with a one-month interval. The vitamin D deficiency was treated with oral colecalciferol 50,000 IU monthly and the vitamin B<sub>12</sub> deficiency with six intramuscular injections of 1 mg hydroxocobalamin. Three weeks after the last ferric carboxymaltose infusion, routine laboratory control revealed severe hypophosphataemia (P 0.22 mmol/l). A week before admission she had suffered from vomiting and diarrhoea, but two days before admission these complaints had passed spontaneously. Upon laboratory testing, the anaemia had resolved (Hb 7.1 mmol/l, ferritin 300 µg/l, vitamin B<sub>12</sub> 226 pmol/l). Other laboratory results were: calcium 2.25 mmol/l, albumin 39 g/l, 25(OH) vitamin D 62 nmol/l, magnesium 0.71 mmol/l, parathyroid hormone (PTH) 24.8 pmol/l and fractional excretion of P 23.7%. During a ten-day admission, she was treated with intravenous sodium glycerophosphate 40 ml three times daily in combination with 15-20 ml oral phosphate solution (1 ml = 67 mg P) once daily. Restoration of phosphate levels to normal levels was hard to achieve. After ten days, she was discharged with a phosphate level of 0.46 mmol/l, which increased to 0.53 mmol/l nine days after discharge with 15 ml oral phosphate supplementation once daily. Two months later, the serum phosphate level had almost returned to normal limits (P 0.70 mmol/l).

#### Case 4

A 47-year-old female of Caribbean origin with known Graves' hyperthyroidism since 1997 was treated medically until 2003. Then, she received radioactive iodine therapy, after which her thyroid function normalised. In December 2012, she was admitted because of severe anaemia (Hb 3.3 mmol/l, MCV 54 fl, ferritin 2 µg/l, transferrin saturation 3 %).

She presented with increased menstrual bleeding due to a small intramural fibroid, fatigue, headache and palpitations. Additionally, she had hypothyroidism (TSH 22.4 mU/l, normal 0.4-4.0 mU/l, free thyroxine 8.8 pmol/l, normal 10.0-24.0 pmol/l). Calcium (2.25 mmol/l), phosphate (0.85 mmol/l), albumin (37 g/l) and kidney function (eGFR >90 ml/min/1.73 m<sup>2</sup>) were normal. Besides oral levothyroxine 50 µg once daily and three units of red blood cell transfusions, she received three gifts of 1000 mg ferric carboxymaltose with a two-week interval between the first two infusions and a one-month interval between the second and third. Four days after the last infusion, routine laboratory control revealed a severe hypophosphataemia (P 0.28 mmol/l). The hypothyroidism had improved (TSH 12.8 mU/l, free thyroxine 10.2 pmol/l) and the anaemia had resolved (Hb 8.9 mmol/l, ferritin 1646 µg/l, transferrin saturation 56 %). Other laboratory results were: calcium 2.25 mmol/l, albumin 38 g/l, magnesium 0.74 mmol/l, 25(OH) vitamin D 49 nmol/l, PTH 9.8 pmol/l and a fractional excretion of P 28.4%. Besides feelings of depression, she had no complaints. She was treated with intravenous sodium glycerophosphate 40 ml and oral phosphate solution (1 ml = 67 mg phosphate) 15 ml three times daily. Serum phosphate increased to 0.50 mmol/l. She was discharged with continuation of oral phosphate solution.

Six weeks afterwards, routine laboratory control again revealed severe hypophosphataemia (P 0.20 mmol/l). She complained of weakness and fatigue and the hypothyroidism had worsened (TSH 30.8 mU/l and free thyroxine 8.3 pmol/l). The level of haemoglobin remained normal. She was treated with 40 ml intravenous sodium glycerophosphate, with an additional 20 ml the next day. Serum phosphate increased to 0.89 mmol/l. Levothyroxine was increased to 100 µg daily.

Six days later, once again, the patient developed hypophosphataemia (P 0.33 mmol/l). Fractional urinary excretion of phosphate was 18%. Once more, she received 20 ml intravenous sodium glycerophosphate for two days, upon which the serum phosphate levels increased to 0.87 mmol/l. In addition, 25(OH) vitamin D was 45 nmol/l with normal levels of serum calcium and magnesium. Unfortunately, the PTH was not determined at that point. The day after admission serum FGF23 level was 119 RU/ml. She was discharged on oral phosphate solution 20 ml three times daily (1 ml = 67 mg phosphate) and colecalciferol 50,000 IU/ml weekly.

In the following month, her serum phosphate levels still remained low with values between 0.41 and 0.63 mmol/l. Due to the worsened hypothyroidism (TSH 72.8 mU/l), compliance of intake of oral phosphate solution seemed disputable. However, the vitamin D deficiency had resolved (25(OH) vitamin D 64 nmol/l) and afterwards the phosphate levels normalised to levels between 0.74 and 0.81 mmol/l.

## DISCUSSION

Many studies show that intravenous ferric carboxymaltose is superior to oral iron supplementation in restoring Hb levels.<sup>1,3,4,8</sup> Furthermore, it has less drug-related adverse effects.<sup>8</sup> However, some clinical studies found a transient, generally non-symptomatic, hypophosphataemia after intravenous iron supplementation. In this paper, we report four cases of severe and symptomatic hypophosphataemia. Despite the fact that concomitant disorders of phosphate homeostasis were present in cases 1, 3 and 4, the serum phosphate levels of all patients were normal or near-normal prior to intravenous iron administration. Therefore, we conclude that the cause of hypophosphataemia must be intravenous iron administration and that hypophosphataemia provoked by intravenous iron supplementation can be severe, symptomatic and prolonged.

Phosphate homeostasis is maintained via the bone-kidney endocrine axis, in which PTH, vitamin D, and FGF23 are important regulators. Renal phosphate excretion is regulated mainly by PTH and FGF23, which are both phosphaturic hormones.<sup>9-11</sup> Hyperparathyroidism was present in cases 1, 3, and 4. In the last two cases this can be attributed to vitamin D deficiency, since calcium was at the lower level of the normal range and renal function was normal. In addition, it seems unlikely that the degree of the hypovitaminosis D, with only a slight upregulation of PTH, can explain the deep hypophosphataemia by itself. Also, all these patients had increased urinary phosphate excretion that was inadequate to the degree of the hypophosphataemia. The inadequate phosphate excretion that was seen could be explained by hyperparathyroidism, but this was not present in case 2. Thus, other mechanisms have to be involved.

Studies have shown that hypophosphataemia induced by intravenous iron administration is mediated by an increase in serum levels of FGF23.<sup>12</sup> In our first case, this was indeed demonstrated, as FGF23 levels and renal phosphate excretion were increased during the second episode of hypophosphataemia after intravenous iron administration. The fourth case showed FGF23 levels at the upper limit of the normal range two months after the last infusion of ferric carboxymaltose. It may be speculated that the level of FGF23 might have been higher in between. On the other hand, the level of FGF23 can be regarded as inadequately high in relation to the degree of the hypophosphataemia. Furthermore, it is interesting to note that in the third case, the level of PTH increased while the vitamin D level normalised. Although levels of FGF23 and calcium were not determined in that case, the increase in PTH could be explained by an increase in FGF23 levels. Studies have shown that the increase in PTH in patients with chronic kidney disease is mediated by FGF23. As FGF23 suppresses the synthesis of calcitriol, it indirectly stimulates PTH

secretion.<sup>13,14</sup> Although FGF23 inhibits PTH secretion in the short term, with continuous stimulation (e.g. during chronic kidney disease) the inhibiting effect of FGF23 on PTH fades away and levels of PTH increase, possibly by downregulation of the FGF23/Klotho receptor complex.<sup>15-17</sup> Thus, the increase in PTH in case 3 may be explained by sustained increase of FGF23 levels following intravenous iron administration.

The FGF23-mediated phosphaturia might also explain the difference in the incidence of hypophosphataemia after ferric carboxymaltose administration between patient populations. In patients with chronic kidney disease, hypophosphataemia is observed in 3.8% of all cases, while in iron deficiency anaemia due to gynaecological diseases, this percentage rises to 70%.<sup>5,8</sup> As patients with chronic kidney disease already have a restricted renal excretion of phosphate and upregulated levels of FGF23, a further increase in FGF23 will have a mild effect on their renal phosphate excretion.<sup>18,19</sup> In patients with a normal glomerular filtration rate, the effect can be much more pronounced as is shown in this report. In particular, when phosphate levels are already relatively low prior to treatment, which can be the case after renal transplantation due to persistent hyperparathyroidism (case 1) or by concomitant vitamin D deficiency (cases 3 and 4), an increase in FGF23 levels may result in a significant hypophosphataemia.

In addition, 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 (cFGF23). This leads to a stable level of active, intact FGF23 (iFGF23).<sup>20,21</sup> Administration of ferric carboxymaltose seems to disrupt this balance by inhibiting the cleavage of iFGF23. Conversely, iron dextran does not have an effect on FGF23 cleavage.<sup>20</sup> These findings may clarify the difference in incidence of hypophosphataemia after administration of different intravenous iron supplements, though the mechanism within the osteocytes remains unclear. In the second case, however, hypophosphataemia occurred to the same degree after both administration of ferric carboxymaltose and iron sucrose. Therefore, development of hypophosphataemia should be considered after administration of different types of intravenous iron preparations.

Finally, it is important to note that intravenous and oral phosphate supplementation may be harmful. It implies a risk of hypocalcaemia, arrhythmias, ectopic calcification, and can induce acute phosphate nephropathy.<sup>22,23</sup> In addition, although the nadir of serum phosphate is usually reached two weeks after intravenous iron administration, this time course can be prolonged.<sup>5-7</sup> Suppression of  $1\alpha$ -hydroxylation of vitamin D, which is one of the effects of FGF23, can last up to three months after the last administration.<sup>24</sup> In the fourth case, hypophosphataemia persisted for up to three months, which may be explained

by this mechanism. Therefore, physicians should be aware of possible adverse effects of phosphate supplementation and a prolonged and recurrent hypophosphataemia.

In order to prevent this potentially life-threatening side effect of intravenous iron administration, we propose routine evaluations of the risk of development of hypophosphatemia prior to treatment with ferric carboxymaltose. Blood analysis should include serum levels of creatinine and phosphate. In patients with a compromised phosphate homeostasis (e.g. patients with a good renal function and low or on the lower end of the normal range serum phosphate), it is advised to measure serum phosphate once more two weeks after commencing treatment, when the phosphate levels reach a nadir. In addition, alternative iron preparations (such as iron dextran) should be considered. However, these imply an increased risk of other side effects, such as allergic reactions in the case of iron dextran.<sup>25</sup>

## CONCLUSION

Clinicians should be aware of this potential complication and carefully evaluate indications for intravenous iron supplementation. Evaluation of pre-existent levels of serum phosphate and renal function is warranted to evaluate the risk of developing hypophosphataemia. In addition, monitoring of phosphate balance should be performed, especially in patients susceptible to a dysregulation of the phosphate homeostasis (e.g. patients with hyperparathyroidism, hypovitaminosis D, pre-existent hypophosphataemia in combination with good renal function). Further research is required to determine whether lower doses of intravenous ferric carboxymaltose or other intravenous iron preparations may be preferable in this patient population.

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