SHORT REPORT

Severe hypophosphataemia following ferric carboxymaltose infusion in paediatric patients with inflammatory bowel disease

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ABSTRACT

This case series describes the cases of three adolescent patients with established inflammatory bowel disease (IBD) who experienced significant hypophosphataemia following intravenous infusion of ferric carboxymaltose as treatment for iron deficiency anaemia. Hypophosphataemia may cause a diverse range of symptoms and may be difficult to diagnose clinically due to their non-specific nature. Checking a baseline phosphate (PO_4) prior to intravenous iron infusion may identify patients at higher risk for significant hypophosphataemia and perhaps allow the selection of an alternative iron preparation. The routine monitoring of PO_4 levels postinfusion presents a greater challenge; with cases of asymptomatic hypophosphataemia likely to be uncovered, as in case 3. Clinicians, patients and families should be aware of the symptoms of hypophosphataemia, and symptomatic patients should have bloods checked to allow prompt identification and correction of abnormalities where required. Review of guidelines surrounding intravenous iron infusion and management of hypophosphataemia in paediatric patients is now required.

CASE SERIES

Case 1

A 17-year-old female patient with established Crohn's disease on thiopurine therapy received intravenous ferric carboxymaltose (1000 mg; 18 mg/kg) due to iron deficiency anaemia (IDA) (haemoglobin 109 g/L), following poor oral iron tolerance and ongoing dizziness and fatigue. She attended the emergency department 3 days following this infusion with abdominal pain, headaches and worsening dizziness.

Her phosphate (PO_4) was 0.67 mmol/L with no recent measurement for comparison. Reduced oral intake secondary to symptoms and weight loss (1.3 kg) were noted on admission (body mass index (BMI) Z-score -0.2); however, no concerns regarding refeeding syndrome were apparent. She was admitted and remained as an inpatient for 11 days with persistent hypophosphataemia despite nine high-dose PO_4 infusions (figure 1). Calcium, renal function, vitamin D and parathyroid hormone (PTH) were within normal limits. The patient was switched to oral therapy for discharge; this was discontinued 20 days postpresentation after PO_4 stabilised. Haemoglobin remained within the low-normal range from 1 month following ferric carboxymaltose infusion (111–127 g/L).

Case 2

A 16-year-old female patient with Crohn's disease and previous right hemicolectomy presented 3 days following ferric carboxymaltose infusion (1000 mg; 18 mg/kg; administered due to IDA (haemoglobin 115 g/L; ferritin 3.9 ug/L)) with severe back pain, muscle weakness and spasms beginning 1 day following infusion. PO_4 was 0.36 mmol/L (Mg and K^+ within normal limits and normal renal function), with normal bone biochemistry 2 months previously (PO_4 1.21 mmol/L). No concerns regarding oral intake were reported (BMI Z-score +0.4). The patient received an intravenous PO_4 infusion, increasing PO_4 to 0.45 mmol/L and resolving symptoms. She was discharged but experienced diarrhoea secondary to oral PO_4 leading to cessation; PO_4 remained persistently low (figure 1).

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Figure 1 Graph demonstrating persistent hypophosphataemia in three patients with paediatric inflammatory bowel disease (cases 1, 2 and 3) following intravenous iron infusion.

despite this and three further intravenous infusions. PTH was normal; calcium remained low to normal throughout this episode (2.09–2.29 mmol/L); vitamin D was found to be low (24 nmol/L) and was replaced as per regional guidelines. Paired urinary and serum electrolytes demonstrated a significantly diminished renal threshold for phosphate. Hypophosphataemia resolved at 8 weeks after initial infusion, with haemoglobin remaining within the low to normal range (121–132 g/L).

Case 3

A 17-year-old female inpatient with an acute flare of ulcerative colitis on intravenous steroid therapy was found to have a PO_4 of 0.44 mmol/L (K^+ 3.3 mmol/L; Mg 0.74 mmol/L; calcium within normal limits; vitamin D and PTH unavailable; no previous PO_4 for comparison). The patient was asymptomatic and managing oral intake with stable weight (BMI Z-score 1.27). Two ferric carboxymaltose infusions had been administered 5 and 4 weeks previously (1 g and 390 mg; 20 mg/kg total dose) due to poor energy levels, IDA (serum iron 8 $\mu\text{mol/L}$, transferrin saturations 13%) and poor

oral iron tolerance. After an infusion of 0.7 mmol/kg sodium phosphate, repeat PO_4 was 0.91 mmol/L and the patient was discharged. Oral PO_4 replacement was commenced after identifying further low PO_4 (0.64 mmol/L) at first outpatient review. This was discontinued after 3 days by the patient due to an increase in gastrointestinal symptoms; however, further review showed stable PO_4 (0.94 mmol/L) despite discontinuation (figure 1). Repeat iron studies 6 weeks following second iron infusion showed low serum iron (5 $\mu\text{mol/L}$) and transferrin saturations (11%).

A fourth patient presenting with symptomatic hypophosphataemia 5 weeks post-ferric carboxymaltose infusion was excluded from this series due to potentially confounding comorbidities.

DISCUSSION

This report describes three adolescent patients within our population who developed hypophosphataemia with intravenous ferric carboxymaltose being the most likely precipitating cause between December 2017 and December 2018. Intravenous iron is increasingly utilised within paediatric inflammatory bowel disease (PIBD) and other diseases for the treatment of IDA, in particular where anaemia is severe or oral iron is poorly tolerated due to gastrointestinal side effects. The Royal Hospital for Children, Glasgow, is one of the largest PIBD units in the UK and is considered a large site as per international criteria, caring for more than 300 patients with PIBD. A recent audit within our department would estimate that this complication occurs in approximately 3%–5% of patients treated with intravenous ferric carboxymaltose. Previous studies have shown intravenous iron to have few reported side effects in paediatrics (table 1). While hypophosphataemia is a recognised side effect of intravenous iron in adults,^{1,2} we believe we report the first potential cases of this within a paediatric population. Patients with mild hypophosphataemia may remain asymptomatic; however, hypophosphataemia may also

Table 1 Summary of studies assessing the safety of ferric carboxymaltose in paediatric practice

Study	Patients (n)	Infusions (n)	Dose (single infusion)	Adverse effects
Papadopoulos <i>et al</i> (2018)	35	58	500–1000 mg	2/35 (5.7% patients; 3.4% infusions) mild rash
Tan <i>et al</i> (2017)	51	Not noted	50–1000 mg	No adverse effects reported
Mantadakis <i>et al</i> (2017)	15	27	500–1000 mg	1/15 (6.7% patients; 3.7% infusions) skin staining secondary to extravasation
Powers <i>et al</i> (2017)	72	116	15 mg/kg; maximum 750 mg	4/72 (5.6% patients; 3.4% infusions) urticaria/pruritus 1/72 (1.4% patients; 0.9% infusions) skin staining secondary to extravasation 1/72 (1.4% patients; 0.9% infusions) tingling localised to cannula site 1/72 (1.4% patients; 0.9% infusions) dyspnoea
Valério de Azevedo <i>et al</i> (2017)	10	10	650–100 mg	1/10 (10.0% patients and infusions) minor headaches 1/10 (10.0% patients and infusions) fever
Laass <i>et al</i> (2014)	72	147	50–1000 mg	2/72 (2.8% patients; 1.4% infusions) mild urticaria 1/72 (1.4% patients; 0.7% infusions) mild oedema of hands and fingers

cause symptoms on a spectrum of severity such as fatigue; muscle weakness, cramps and spasm; myalgia; paraesthesia; seizures and arrhythmia.³ Chronic hypophosphataemia has long-term implications, including effects on bone health; and is therefore of critical importance in the paediatric population.³ The non-specific nature of the aforementioned symptoms means that hypophosphataemia secondary to iron infusion may be difficult to diagnose unless specifically suspected and symptoms may be attributed to other conditions, such as active IBD or IDA itself.

Although the mechanism of hypophosphataemia secondary to intravenous iron is not fully clear, the involvement of fibroblast growth factor 23 (FGF-23), a phosphatonin secreted from osteocytes and osteoblasts, has been suggested.¹ Parenteral iron has been shown to increase levels of active FGF-23 resulting in inhibition of renal PO_4 reabsorption and consequent PO_4 wasting,¹ with the low point of serum PO_4 occurring approximately 2 weeks following iron infusion and hypophosphataemia persisting for a median time of 84 days.⁴ Calculation of PO_4 excretion using paired urinary and serum electrolytes, as undertaken in case 2, may highlight a diminished renal PO_4 threshold following intravenous iron infusion.⁴ Patients receiving ferric carboxymaltose are at higher risk of developing hypophosphataemia and more severe hypophosphataemia when compared with other intravenous iron preparations,¹² but with a lower risk of hypersensitivity reactions.² We speculate that a pharmacogenomic relationship is present in patients with mutations in FGF genes or altered gene expression in those who develop this complication. This hypothesis would need to be explored in a larger number of patients.

While all of these cases were female, there is no compelling biological reason why females are more likely to develop hypophosphataemia following intravenous iron; it is worth noting, however, that severe iron deficiency is more common in females with IBD.⁵ Previous reports suggest that low preinfusion PO_4 is a risk factor for the development of severe hypophosphataemia following intravenous iron.¹ All three patients described above required intravenous PO_4 replacement; with one requiring a prolonged inpatient stay (11 days) for repeated intravenous infusions and another requiring multiple readmissions due to refractory hypophosphataemia. Checking a baseline PO_4 prior to intravenous iron infusion may identify at-risk patients and perhaps allow dose reduction or use of an alternative intravenous iron preparation, potentially reducing the incidence of significant postinfusion hypophosphataemia. The routine monitoring of PO_4 levels following intravenous iron infusion presents a greater challenge; this is likely to uncover cases of asymptomatic hypophosphataemia, as within case 3, and raises the complex question of how and when to treat this. Spurious hypophosphataemia should be considered, especially in asymptomatic patients, and it is important

to investigate other aetiologies of hypophosphataemia such as vitamin D deficiency or refeeding syndrome; in particular for malnourished patients who are also proportionally more likely to require intravenous iron supplementation.⁵

CONCLUSION/LEARNING POINTS

- ▶ Clinicians, patients and their families should be made aware of hypophosphataemia as a side effect of intravenous iron therapy to increase symptom vigilance.
- ▶ Hypophosphataemia should be considered in patients presenting with symptoms such as fatigue, generalised muscle weakness and myalgia following intravenous iron infusion; symptoms should trigger blood monitoring with prompt correction of electrolyte abnormalities undertaken if required.
- ▶ Further investigation into the prevalence of hypophosphataemia following intravenous ferric carboxymaltose in paediatric patients is required.

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