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Severe Symptomatic Hypophosphataemia as a Complication of Parenteral Iron Replacement

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ABSTRACT

Parental iron replacement is given to patients with severe iron deficiency or intolerance to oral iron. Hypophosphataemia has been reported to occur as a complication of parental iron replacement, and is postulated to be related to the carbohydrate moieties used in the parenteral preparations. Hypophosphataemia is under-diagnosed as symptoms such as fatigue, muscle weakness and poor effort tolerance mimic anaemia. Severe hypophosphataemia (<0.32 mmol/l) can result in significant complications such as confusion, rhabdomyolysis and arrhythmias. We report a patient with recurrent admissions for non-specific symptoms attributed to iron deficiency anaemia who received multiple doses of parenteral ferric carboxymaltose (FCM). He was found to have severe hypophosphataemia, with further evaluation showing increased renal phosphate wasting and elevated serum levels of fibroblast-growth-factor 23 (FGF23). FCM was stopped and he was given high-dose oral iron supplementation, with no further episodes of hypophosphataemia.

LEARNING POINTS

- The carbohydrate moieties used in parenteral iron preparations are different, and may have a dose-dependent relationship with the development of hypophosphataemia.
- The mechanism by which hypophosphataemia occurs after parenteral iron replacement is related to increased serum levels of FGF23, which increases renal phosphate wasting.
- The serum phosphate levels of patients receiving parenteral iron replacement (especially ferric carboxymaltose or iron polymaltose) should be routinely monitored for hypophosphataemia, which is an under-diagnosed complication.

KEYWORDS

Hypophosphataemia, parenteral iron replacement, FGF23-mediated renal phosphate wasting

CASE DESCRIPTION

A 70-year-old Asian man with chronic recurrent gastrointestinal bleeding from gastric antral vascular ectasia (GAVE), presented to the emergency department with worsening lethargy and dizziness 2 weeks after receiving parenteral ferric carboxymaltose (FCM) for iron-deficiency anaemia. There was no chest discomfort, breathlessness, focal weakness, vomiting, diarrhoea or evidence of gastrointestinal bleeding.

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Clinical examination and a 12-lead electrocardiogram were unremarkable. There were no focal neurological findings. The patient required admission for intravenous phosphate replacement as he had a serum phosphate level of <0.32 (normal range 0.94–1.50) mmol/l. Renal function, magnesium, calcium and creatinine kinase levels were normal. There were no clinically apparent causes for hypophosphataemia. Haemoglobin remained low (7.5 g/dl), so he was given another dose of FCM.

He had persistent lethargy and dizziness, and remained hypophosphataemic despite intravenous (total 90 mmol) and oral phosphate replacement. The ratio of tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR) was low at 0.36 mmol/l based on the Walton and Bijvoet nomogram [1] (normal age-based range 0.8–1.35), indicating renal phosphate wasting. The 25-hydroxyvitamin D level was normal at 29.3 ng/ml. Serum fibroblast-growth-factor 23 (FGF23), a phosphaturic peptide hormone secreted by osteocytes, was elevated at 220 relative units (RU)/ml (normal range ≤180 RU/ml).

The patient was started on daily calcitriol 0.25 µg, cholecalciferol 1000 IU, and oral Fleet phospho-soda containing 515 mg of phosphate. Serum phosphate levels normalized and oral phosphate replacement was stopped 11 weeks later. As FCM had been reported to cause severe hypophosphataemia [2–4], the patient was started on high-dose oral iron. Serum phosphate levels remained normal without further replacement.

The patient had received 26 doses of parenteral FCM in the previous 3 years, with admissions for non-specific symptoms (palpitations, chest discomfort, lethargy) which had been attributed to anaemia. These symptoms could have been exacerbated by undiagnosed hypophosphataemia.

DISCUSSION

Parenteral iron is used in patients with severe iron deficiency or intolerance to oral iron. Iron deficiency physiologically stimulates increased FGF23 transcription in osteocytes, with a counter-regulatory increase in post-translational FGF23 degradation [2]. FGF23 enhances urinary phosphate excretion and suppresses 1,25-dihydroxyvitamin D levels [2], and parenteral iron administration raises FGF23 level by inhibiting its degradation [3, 4], resulting in hypophosphataemia.

Hardy et al. reported transient hypophosphataemia in 38/78 (49%) patients who received FCM, which was severe (<0.32 mmol/l) in five. In contrast, only 22/52 (22%) patients who received parenteral iron sucrose developed hypophosphataemia, which was severe in none. There was no difference, including in ferritin, vitamin D and haemoglobin levels, between patients except for a higher cumulative iron dose. Schouten et al. [4] described a rapid decrease in renal phosphate reabsorption and resultant hypophosphataemia which persisted for up to 3 weeks after the administration of intravenous iron polymaltose. These findings suggest that the development of hypophosphataemia may be related to the carbohydrate moieties [5] used in parenteral iron preparations, with a possible dose-dependent relationship.

Hypophosphataemia is a common complication of parenteral iron replacement which manifests with non-specific symptoms that mimic anaemia and therefore may remain undiagnosed and untreated for a significant period, especially with regular iron administration. Severe hypophosphataemia with resulting depletion of adenosine triphosphate, however, can result in metabolic encephalopathy, rhabdomyolysis, impaired myocardial contractility, cardiac arrhythmias and respiratory failure due to diaphragmatic weakness. The occurrence of these complications can have a significant impact on patient mortality, morbidity and quality of life. We aim to increase awareness of hypophosphataemia as a consequence of parenteral iron replacement and suggest routine monitoring of serum phosphate levels in patients, especially those who receive FCM or iron polymaltose.

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