Intravenous iron isomaltoside (Monofer)–induced hypophosphataemia: a case report

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Hong Kong Med J 2022;28:267–9
https://doi.org/10.12809/hkmj219354

Case report

In January 2019, an 85-year-old woman with a history of osteoporosis and collapsed L1 had gastric antral vascular ectasia with multiple failed attempts of argon photo-coagulation, resulting in severe iron deficiency anaemia (haemoglobin 4 g/dL). The patient had been repeatedly admitted for congestive heart failure precipitated by anaemia that required blood transfusion. In view of her severe and ongoing blood loss, intravenous iron isomaltoside (Monofer) 800 mg monthly was started in February 2019. Before commencement of iron isomaltoside, iron saturation was 5% (normal 15%-50%). She was optimally nourished with normal serum calcium (2.27 mmol/L; normal 2.15-2.55 mmol/L), phosphate (1.4 mmol/L; normal 0.8-1.5 mmol/L), alkaline phosphatase (108 IU/L; normal 53-141 IU/L) and vitamin D level (79 nmol/L; normal 50-220 nmol/L). Hypophosphataemia (0.5 mmol/L) was first noted in June 2019 (Fig). Owing to the patient's history of collapsed vertebra, she was given a first dose of denosumab in October 2019 by a private orthopaedic surgeon but serum phosphate further worsened to 0.1 mmol/L despite aggressive oral phosphate replacement. She refused hospital admission at this time. In December 2019, the patient was hospitalised for anaemia and hypophosphataemia (0.4 mmol/L) with concomitant serum calcium 2.07 mmol/L and alkaline phosphatase 199 IU/L. Her estimated glomerular filtration rate was

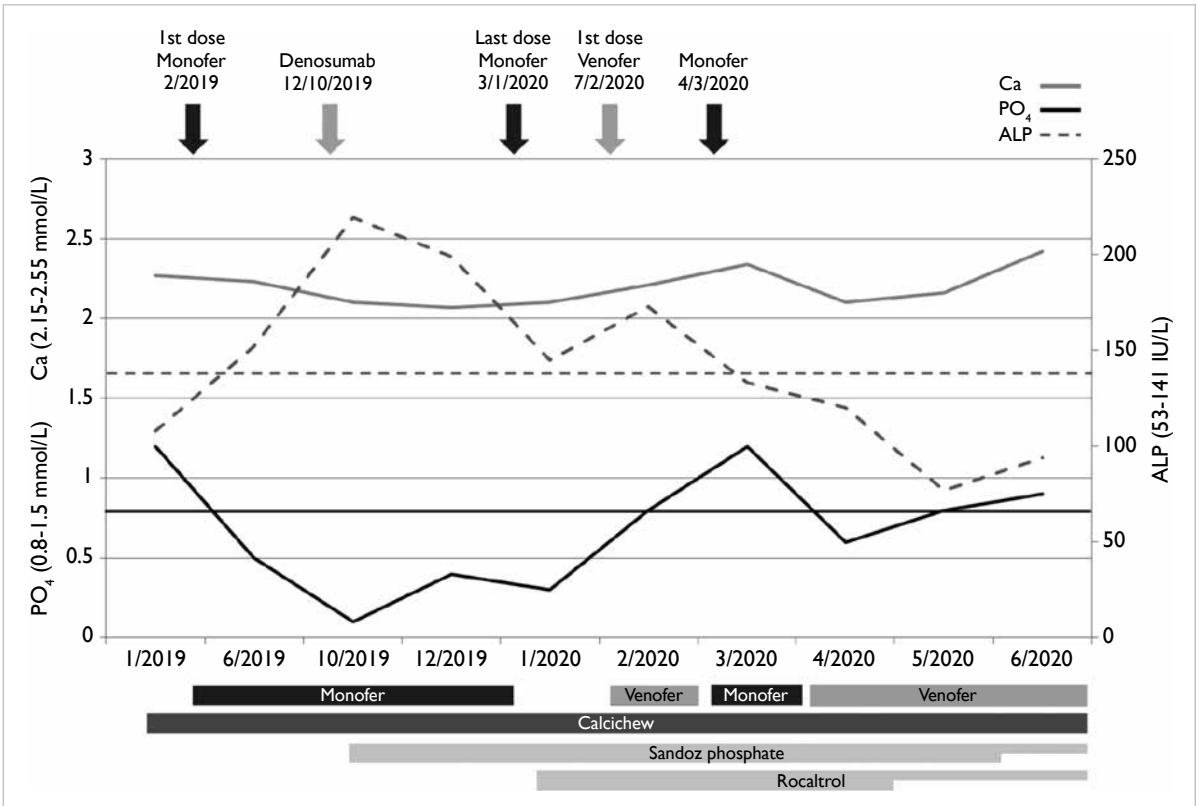

FIG. Changes in serum calcium (Ca), phosphate (PO_4) and alkaline phosphatase (ALP) levels before and after administration of intravenous iron and denosumab

>90 mL/min/1.73 m^2. Fractional excretion of phosphate confirmed renal phosphate wasting (FePO4 14%; normal <5%) and bicarbonate was 30 mmol/L (normal 22-26 mmol/L). Urinary protein and glucose were negative. Iron saturation was 24% and parathyroid hormone 22.6 nmol/L (normal 1.6-7.2 nmol/L). Fibroblast growth factor 23 (FGF23), measured 3 weeks after the last dose of iron isomaltoside, was 155 IU/mL (normal <188 IU/mL). Intravenous iron-induced hypophosphataemia was suspected. Iron isomaltoside was stopped and rocaltrol was commenced in January 2020 with prompt improvement in phosphate level. Another intravenous iron preparation, iron sucrose (Venofer), was started due to her severe anaemia. Attempted re-challenge with iron isomaltoside resulted in recurrent hypophosphataemia. Rocaltrol and phosphate sandoz were gradually tapered down over 6 months. Serum phosphate remained normal while on iron sucrose and denosumab.

Discussion

Iron deficiency anaemia is a commonly encountered problem in daily practice. Although oral iron remains the recommended route of replacement due to its low cost and availability, intravenous iron is considered superior in several respects. First, the gastrointestinal side-effects of oral iron are avoided. Second, bioavailability is improved where that of oral iron is reduced in conditions such as achlorhydria (eg, proton pump inhibitors, gastric bypass), small bowel malabsorption (eg, inflammatory bowel disease, prior small bowel resection, celiac disease) and chronic inflammation (via upregulation of hepcidin). Third, intravenous iron allows rapid repletion of iron, making it a more suitable choice when there is severe and/or ongoing blood loss.

The new-generation intravenous iron preparations are all stable iron-carbohydrate complexes. The three commonly used intravenous iron preparations locally are iron carboxymaltose (Ferinject), iron isomaltoside (Monofer) and iron sucrose (Venofer). They differ in the attaching carbohydrate ligands that affect the capacity, stability and immunogenicity of the complex. Hypophosphataemia is a well-described complication of iron carboxymaltose but is far less common in the other two preparations: the incidence[1] of hypophosphataemia is 58%, 4% and 1% for patients with preserved renal function given iron carboxymaltose, iron isomaltoside and iron sucrose, respectively. In addition, iron carboxymaltose–induced hypophosphataemia can be severe and protracted resulting in osteomalacia and multiple fractures. Although the pathogenesis[2] is not fully understood, it is believed to be mediated through iron carboxymaltose–induced production of biologically active intact FGF23. The FGF23 is a phosphaturic hormone produced by osteocytes and osteoblasts. It reduces phosphate reabsorption by downregulation of sodium-phosphate co-transporter in the proximal renal tubule. The FGF23 also inhibits 1,25-dihydroxyvitamin D synthesis, leading to vitamin D deficiency and secondary hyperparathyroidism that contribute to reduced intestinal phosphate uptake and further increased renal phosphate wasting, respectively. Iron isomaltoside also increases intact FGF23 secretion, but to a much lesser extent than iron carboxymaltose.[3] Again, such difference is speculated to be due to the carbohydrate ligand, since iron carboxymaltose and iron isomaltoside are equally effective in replenishing iron store. Although other indicators of proximal renal tubular dysfunction such as fractional excretion of urate and urine amino acid were not measured in this patient, the absence of glycosuria and non-suppressed FGF23 level were not typical of a diagnosis of renal Fanconi syndrome. In addition, improved serum phosphate level after stopping iron isomaltoside supported the diagnosis of iron-induced phosphaturia in this patient.

In the meta-analysis by Schaefer et al,[4] low baseline iron saturation and normal renal function were identified as positive predictors of iron-induced hypophosphataemia; both were present in this patient. Severe iron deficiency may cause a higher increase in FGF23 transcription and renal impairment is protective due to intrinsic kidney resistance to FGF23. Furthermore, denosumab may have worsened the pre-existing hypophosphataemia induced by iron isomaltoside in this patient since serum phosphate level fell abruptly in October 2019, 1 week after denosumab injection. Denosumab is an anti-RANKL (receptor activator of nuclear factor-κB ligand) antibody that inhibits osteoclastic activity and hence bone resorption. Severe hypophosphataemia caused by denosumab has been described in a patient with tenofovir-induced osteomalacia[5] and is possibly mediated through the following two mechanisms: first, decreased bone resorption directly reduces phosphate release; second, fall in bone-derived calcium worsens secondary hyperparathyroidism that in turn enhances phosphaturia. These may explain the profound hypophosphataemia in this patient after denosumab injection.

There are several reasons for the normal FGF23 level in this patient. First, the commercial FGF23 assay detects both intact and cleaved FGF23; an increased intact FGF23 together with a reduced cleaved FGF23 may result in a "normal" FGF23 level. Second, FGF23 may have dropped significantly 3 weeks after the last dose of iron isomaltoside. Third, FGF23 transcription was reduced with correction of iron deficiency as reflected by the normal iron

saturation.

In addition to phosphate replacement and switching to a less phosphaturic intravenous iron preparation, activated vitamin D is needed to increase phosphate reabsorption during the initial phase, even in a patient with preserved renal function. This is because FGF23 inhibits renal activation of 25-dihydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D.

In conclusion, although hypophosphataemia is much less common in patients on iron isomaltoside than iron carboxymaltose, it is advisable to monitor phosphate level 1 to 2 weeks after iron isomaltoside injection in high-risk patients, such as those with severe anaemia who require repeat dosing, and patients with pre-existing vitamin D deficiency and/or hyperparathyroidism.

Author contributions

All authors contributed to the concept, acquisition of data, interpretation of data, drafting of the manuscript, and critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed consent for the treatment/procedures and publication.

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