Three cases of significant hypophosphataemia associated with intravenous iron

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Objective

Intravenous (IV) administration of iron allows rapid replacement in cases of severe iron deficiency anaemia. It is frequently used where oral supplementation is ineffective or intolerable. Three cases of significant hypophosphataemia associated with IV iron recently occurred in our hospital. Improved awareness of risk factors and subsequent symptoms may prevent further cases of hypophosphataemia, and result in more rapid assessment and treatment for patients who develop symptoms.

What is the big deal about hypophosphataemia?

Physiological phosphate is essential for life.
It is necessary for:

- Bone structure
- Intracellular energy storage and release
- Red cell haemoglobin binding and release of oxygen
- Nucleic acid production
- Lipid bilayer formation

Serum phosphate levels	
Usual range	0.9 – 1.6 mmol/L
Hypophosphataemia	0.8 mmol/L or less
Severe hypophosphataemia	0.6 mmol/L or less
Life-threatening hypophosphataemia	0.3 mmol/L or less

Risk factors for hypophosphataemia include:

- Intracellular shift of phosphate due to
  - respiratory alkalosis, or
  - carbohydrate administration following starvation (refeeding syndrome)
- Decreased intestinal absorption (may be drug-induced with chronic ingestion of antacids or phosphate binders)
- Decreased dietary intake with chronic alcoholism or anorexia nervosa
- Increased cellular demand for phosphate during acute acceleration of erythropoiesis
- Urinary phosphate-wasting syndromes

Symptoms
are mostly due to intracellular phosphate depletion, and usually don't occur until hypophosphataemia is severe. Red cell 2,3-diphosphoglycerate levels fall, reducing haemoglobin affinity for oxygen and decreasing oxygen release into tissue. Intracellular adenosine triphosphate (ATP) levels also fall, so energy-dependent cell functions are compromised.

Significant hypophosphataemia may manifest as:

- Metabolic encephalopathy, from mild irritability and parasthesias to delirium, seizures, coma
- Impaired myocardial contractility, ventricular arrhythmias
- Impaired diaphragmatic contractility
- Proximal myopathy
- Dysphagia, ileus

Registered product information for IV iron preparations includes hypophosphataemia as a known adverse effect. Ferinject® has also recently included hypophosphataemia "which in most cases is transient and without clinical symptoms" in *Special Warnings and Precautions for Use*.

At the time our cases presented, the Therapeutic Goods Administration's Database of Adverse Events Notifications (DAEN) contained only 21 reports of hypophosphataemia associated with parenteral iron products in Australia.

International case reports indicate that patients with existing hyperparathyroidism, vitamin D deficiency, and nutritional conditions leading to decreased absorption or intake of phosphate are at higher risk of hypophosphataemia after administration of IV iron.

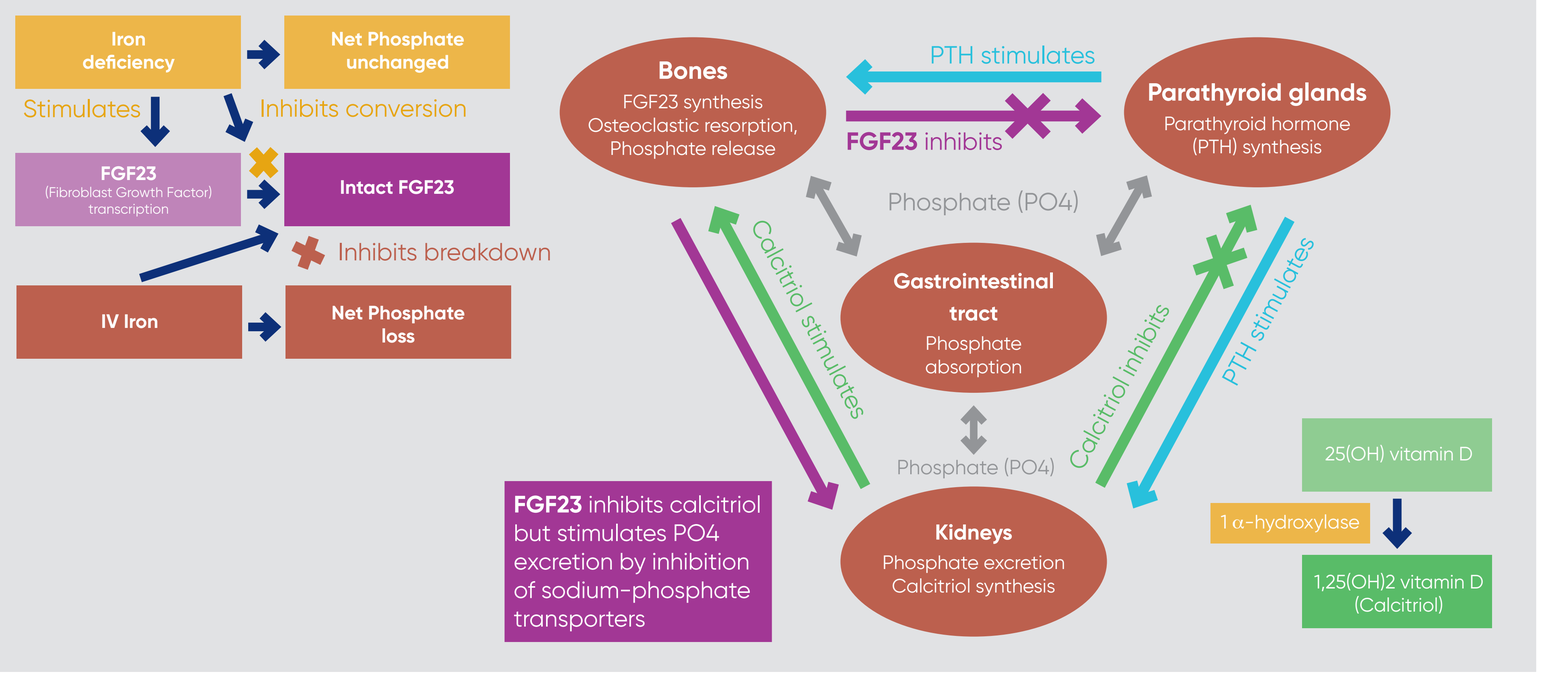
Cases

Prior to administration of IV iron, all three cases were:

- Iron deficient and
- Vitamin D deficient and
- Intolerant of oral iron supplements (or these were ineffective)

Ferric carboxymaltose 1000 mg IV infusion was administered. All three patients have since recovered from hypophosphataemia with appropriate treatment and ongoing management.

Figure 1 – Effect of IV iron on renal phosphate excretion



Case 1

A 23-year old woman with past history of iron deficiency.

- Recent endoscopy was normal, coeliac screen negative, menstruation light and regular
- Previous phosphate and calcium levels were consistently within normal range
- Presented to the Emergency Department complaining of headache, myalgia, palpitations, nausea, vomiting and diarrhoea
- Symptoms commenced one day after IV iron
- Serum phosphate on presentation was 0.27 mmol/L
- **Rx** IV phosphate, then oral phosphate and colecalciferol.
- Diarrhoea and vomiting prevented continuation of oral supplements
- Readmission was required:
  - One week in hospital
  - Multiple doses of IV phosphate
  - Levels did not rise above 0.7 mmol/L
  - Ongoing exhaustion and feeling "twitchy"

Physician impression:

- *Low phosphate secondary to elevated FGF 23, causing*
- *Phosphaturia (confirmed by 12 hour urinary phosphate) and*
- *Impaired 1 α-hydroxylation of vitamin D, exacerbated by low 25(OH) vitamin D*
- *Prognosis of weeks to months to resolve*
- **Rx** Calcitriol, colecalciferol and spaced doses of oral phosphate.

Cases 2 and 3

Two pregnant women in their 30's with:

- Iron deficiency anaemia
- Hyperemesis gravidarum and
- Vitamin D deficiency

Both experienced:

- Ongoing fatigue after IV iron, and
- Ongoing breathing difficulty soon after IV iron

Case 2 also had daily chest pain.

Serum phosphate levels

Case 2. 0.58 mmol/L

Case 3. 0.64 mmol/L

Tests for each patient revealed increased urinary phosphate excretion.

Mechanism

Regulation of phosphate is complex, and dependent on acute and chronic processes involving:

- Gastrointestinal absorption
- Parathyroid hormone synthesis and release
- Osteoclastic resorption
- Fibroblast growth factor 23 (FGF23) synthesis and activation
- Calcitriol synthesis
- Renal excretion and reabsorption of phosphate
- Numerous other factors

Mechanism (cont'd)

Calcitriol synthesis is dependent upon availability of 25(OH) vitamin D and action of 1 α-hydroxylase. All of our cases had vitamin D deficiency prior to IV iron. Iron deficiency stimulates transcription of FGF23, but inhibits conversion to active intact FGF23 (iFGF23), with no net change in serum phosphate levels. IV iron preparations appear to inhibit breakdown of iFGF23, causing a transient increase in iFGF23 which induces phosphate excretion by inhibition of renal sodium-phosphate transporters, and suppresses production of calcitriol. See Figure 1.

Pharmacist Interventions

Pharmacists may aid in prevention of hypophosphataemia associated with IV iron, and management of patients who develop symptoms after administration by:

- Identifying patients at higher risk of development of hypophosphataemia
- Identifying and referring patients with ongoing fatigue or other symptoms suggestive of hypophosphataemia after IV iron
- Reporting suspected adverse drug reactions
- Ensuring local policies and procedures include risk factors and symptoms of hypophosphataemia

Conclusion

Hypophosphataemia associated with IV iron is not frequently reported to DAEN and may be under-recognised.

Morbidity may be reduced by correction of known modifiable risk factors prior to IV iron and investigation of reported fatigue after IV iron.

Post infusion phosphate levels should be monitored in patients with existing hyperparathyroidism, vitamin D deficiency, and nutritional conditions leading to decreased absorption or intake of phosphate.

Key References

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