Low phosphate after modern intravenous iron? Fibroblast growth factor 23 may be the key!

Iron is an essential substance with a number of roles in the body. Anaemia caused by low iron (iron deficiency anaemia) can worsen disease outcomes and reduce the quality of people's lives. Iron deficiency anaemia can be treated with iron given through the mouth (orally) or through the vein (intravenous). Intravenous iron can be useful when large doses are needed, or where there is trouble administering oral iron.

Modern intravenous iron preparations (e.g. ferumoxytol, ferric carboxymaltose, and ferric derisomaltose) are commonly used to treat iron deficiency anaemia and are considered safe and effective. They can be given at high doses on a single visit, therefore potentially saving time for the patients and the service. However, a distinct side effect appears to develop more frequently after ferric carboxymaltose is given, resulting in low phosphate (hypophosphataemia).

Phosphate is essential for the way cells work, the production of energy and the means by which cells communicate. Most of the phosphate in the body exists in the bones of the skeleton. How quickly low phosphate develops affects the symptoms we observe: acute (fast-developing) hypophosphataemia causes tiredness, weakness, abnormal heart rhythms and breathing, and neurological problems including seizures. Chronic (slow-developing) hypophosphataemia is associated with weak bones that easily break and weak muscles.

Initially, scientists believed that the cause of hypophosphataemia was the fact that phosphate was needed for the creation of red blood cells after giving iron. However, recent studies suggest that hypophosphataemia develops because of fibroblast-growth-factor 23, a hormone that is important in the management of phosphate in the body. Fibroblast-growth-factor 23 increases the amount of phosphate in the urine by working on special receptors in the kidneys (NaPi-2a, NaPi-2c) while also decreasing the amount of active vitamin D (calcitriol) by stopping an important step in its formation. Less active vitamin D means that less phosphate is absorbed from the intestines.

Research suggests that hypophosphataemia is more common in patients receiving ferric carboxymaltose. More specifically a statistical analysis that combined the results of 42 studies using either ferric derisomaltose or ferric carboxymaltose found out that hypophosphataemia occurred more often with ferric carboxymaltose than ferric derisomaltose and that the overall level of phosphate was lower with ferric carboxymaltose than ferric derisomaltose. Another review of recent studies commented on the fact that ferric carboxymaltose causes low phosphate concentrations more often than other intravenous irons that are available in the USA. A review of 45 studies including ferric carboxymaltose indicated that almost four out of ten patients receiving this preparation can develop mildly low phosphate. Studies comparing ferric carboxymaltose head-to-head with other modern intravenous iron preparations found similar findings. It is important to state that the frequency of symptoms were not necessarily explored, and that not all cases had

symptoms.

Scientists believe that the reason that ferric carboxymaltose and other similar irons lead to hypophosphataemia is related with the breakdown of fibroblast-growth-factor 23. It appears that ferric carboxyaltose blocks the breakdown of fibroblast-growth-factor 23 leading to more active fibroblast growth factor 23 circulating in the body. As a result, the patient loses more phosphate in the urine, and takes in less phosphate from the gut.

It is important for healthcare professionals to monitor certain blood tests before giving iron, such as ferric caboxymaltose and those include baseline phosphate, vitamin D and severity of iron deficiency anaemia, as those have been linked with increased chance of getting low phosphate. The healthcare professional should also explain this side effect to the patient and ensure that phosphate is monitored around 2 weeks after giving iron, or if the patient develops any symptoms.

Xenophon Kassianides
Hull University Teaching Hospitals NHS Trust and the Hull York Medical School, United Kingdom

Publication

Hypophosphataemia, fibroblast growth factor 23 and third-generation intravenous iron compounds: a narrative review
Xenophon Kassianides, Sunil Bhandari
Drugs Context. 2021 Jan 19